Chapter 6 Adverse Drug Effects

Adverse effect is 'any undesirable or unintended consequence of drug administration'. It is a broad term, includes all kinds of noxious effect—trivial, serious or even fatal.

For the purposes of detecting and quantifying only those adverse effects of a drug which are of some import and occur in ordinary therapeutic setting, the term *adverse drug reaction* (ADR) has been defined as 'any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug'. This definition excludes trivial or expected side effects and poisonings or overdose.

Another term *'adverse drug event'* (ADE) has been used to mean 'any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with the treatment'. The idea is to record all adverse events first, and look for causality only while analyzing pooled data.

All drugs are capable of producing adverse effects, and whenever a drug is given a risk is taken. The magnitude of risk has to be considered along with the magnitude of expected therapeutic benefit in deciding whether to use or not to use a particular drug in a given patient, e.g. even risk of bone marrow depression may be justified in treating cancer, while mild drowsiness caused by an antihistaminic in treating common cold may be unacceptable.

Adverse effects may develop promptly or only after prolonged medication or even after stoppage of the drug. Adverse effects are not rare; an incidence of 10–25% has been documented in different clinical settings. They are more common with multiple drug therapy and in the elderly. Adverse effects have been classified in many ways. One may divide them into:

Predictable (Type A or Augmented) reactions

(mechanism based adverse reactions)   These are based on the pharmacological properties of the drug, which means that they are augmented, but qualitatively normal response to the drug; include side effects, toxic effects and consequences of drug withdrawal. They are more common, dose related and mostly preventable and reversible.

Unpredictable (Type B or Bizarre) reactions

These are based on peculiarities of the patient and not on drug's known actions; include allergy and idiosyncrasy. They are less common, often non-dose related, generally more serious and require withdrawal of the drug. Some of these reactions can be predicted and prevented if their genetic basis is known and suitable test to characterize the individual's phenotype is performed.

Severity of adverse drug reactions   has been graded as:

Minor: No therapy, antidote or prolongation of hospitalization is required.

Moderate: Requires change in drug therapy, specific treatment or prolongs hospital stay by atleast one day.

Severe: Potentially life-threatening, causes permanent damage or requires intensive medical treatment.

Lethal: Directly or indirectly contributes to death of the patient.

Pharmacovigilance

Pharmacovigilance has been defined by the WHO (2002) as the 'science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.' The information generated by

pharmacovigilance is useful in educating doctors about ADRs and in the official regulation of drug use. Its main purpose is to reduce the risk of drug-related harm to the patient. It has an important role in the rational use of medicines, as it provides the basis for assessing safety of medicines.

The activities involved in pharmacovigilance are:

a. Postmarketing surveillance and other methods of ADR monitoring such as voluntary reporting by doctors (e.g. yellow card system of UK), prescription event monitoring, computerized medical record linkage and other cohort/case control studies as well as anecdotal case reports by doctors.

Voluntary reporting depends on the initiative and willingness of the health professionals. It is minimal in India, while even in the developed countries only ~10% ADRs are reported voluntarily. Generally, immediately occurring reactions and those that are dramatic are reported. Though even rare reactions can be detected by this method, it does not provide incidence of the reaction.

b. Dissemination of ADR data through 'drug alerts', 'medical letters,' advisories sent to doctors by pharmaceuticals and regulatory agencies (such as FDA in USA, committee on safety of medicines in UK).

c. Changes in the labelling of medicines indicating restrictions in use or statuary warnings, precautions, or even withdrawal of the drug, by the regulatory decision making authority.

Pharmacovigilance centres have been set up in most countries. The Uppsala Monitoring Centre (Sweden) is the international collaborating centre. In India, the Central Drugs Standard Control Organization (CDSCO) is coordinating the pharmacovigilance programme, under which peripheral, regional and zonal monitoring centres have been set up along with a National Pharmacovigilance advisory committee. The pharmacovigilance centres collect, communicate and disseminate ADR data by linking with hospitals as well as practitioners and are also expected to provide expertise for assessing causality and severity of ADRs by using standard algorithms and rating scales like the 'Naranjo algorithm' (causalilty assessment) and modified Hartwig scale (severity grading).

Causality assessment

When a patient undergoing drug therapy experiences an adverse event, it may be due to the drug, or the disease or some other causes. Most of the time, a clear-cut 'yes/no' cause and effect relationship between a drug and the adverse event cannot be pronounced. Causality is assessed on the basis of:

- *Temporal relationship:* How the time-sequence of the event is related to drug administration.
- *Previous knowledge:* Whether the drug is known to produce the event in earlier recipients with a certain degree of consistency.
- *Dechallenge:* Whether the event subsided on stopping the drug.
- *Rechallenge:* Whether the event reappeared when the drug was administered again after a gap during which the event had subsided. Many times rechalenge is unethical/dangerous, and is not done.

Assessed on the basis of the above criteria, causality has been graded as:

1. *Definite:* Causality is proven.
2. *Probable:* Though not proven, drug is the likely cause of the event.
3. *Possible:* Drug as well as other causes could be responsible for the event.
4. *Doubtful:* Drug unlikely to be the cause, but cannot be ruled out.

Prevention of adverse effects to drugs

Adverse drug effects can be minimized but not altogether eliminated by observing the following practices:

1. Avoid all inappropriate use of drugs in the context of patient's clinical condition.
2. Use appropriate dose, route and frequency of drug administration based on patient's specific variables.
3. Elicit and take into consideration previous history of drug reactions.
4. Elicit history of allergic diseases and exercise caution (drug allergy is more common in patients with allergic diseases).
5. Rule out possibility of drug interactions when more than one drug is prescribed.
6. Adopt correct drug administration technique (e.g. intravenous injection of vancomycin must be slow).
7. Carry out appropriate laboratory monitoring (e.g. prothrombin time with warfarin, serum drug levels with lithium).

Adverse drug effects may be categorized into:

1. Side effects

These are unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses. Generally, they are not serious, can be predicted from the pharmacological profile of a drug and are known to occur in a given percentage of drug recipients. Reduction in dose, usually ameliorates the symptoms.

A side effect may be based on the same action as the therapeutic effect, e.g. atropine is used in preanaesthetic medication for its antisecretory action. The same action produces dryness of mouth as a side effect. Glyceryl trinitrate relieves angina pectoris by dilating peripheral vasculature which is also responsible for postural hypotension and throbbing headache.

The side effect may also be based on a different facet of action, e.g. promethazine produces sedation which is unrelated to its antiallergic action; estrogens cause nausea which is unrelated to their antiovulatory action.

An effect may be therapeutic in one context but side effect in another context, e.g. codeine used for cough produces constipation as a side effect, but the latter is its therapeutic effect in traveller's diarrhoea; depression of A-V conduction is the desired effect of digoxin in atrial fibrillation, but the same may be undesirable when it is used for CHF.

Many drugs have been developed from observation of side effects, e.g. early sulfonamides used as antibacterial were found to produce hypoglycaemia and acidosis as side effects which directed research resulting in the development of hypoglycaemic sulfonylureas and carbonic anhydrase inhibitor—acetazolamide.

2. Secondary effects

These are indirect consequences of a primary action of the drug, e.g. suppression of bacterial flora by tetracyclines paves the way for superinfections; corticosteroids weaken host defence mechanisms so that latent tuberculosis gets activated.

3. Toxic effects

These are the result of excessive pharmacological action of the drug due to overdosage or prolonged use. Overdosage may be absolute (accidental, homicidal, suicidal) or relative (i.e. usual dose of gentamicin in presence of renal failure). The manifestations are predictable and dose related. They result from functional alteration (high dose of atropine causing delirium) or drug induced tissue damage (hepatic necrosis from paracetamol overdosage). The CNS, CVS, kidney, liver, lung, skin and blood forming organs are most commonly involved in drug toxicity.

Toxicity may result from extension of the therapeutic effect itself, e.g. coma by barbiturates, complete A-V block by digoxin, bleeding due to heparin.

Another action of the drug can also be responsible for toxicity, e.g.—
- Morphine (analgesic) causes respiratory failure in overdosage.
- Imipramine (antidepressant) overdose causes cardiac arrhythmia.
- Streptomycin (antitubercular) causes vestibular damage on prolonged use.

Poisoning   In a broad sense, poisoning implies harmful effects of a chemical on a biological system. It may result from large doses of drugs because 'it is the dose which distinguishes a drug from a poison'. *Poison* is a 'substance which endangers life by severely affecting one or more vital functions'. Not only drugs but other household and industrial chemicals, insecticides, etc. are frequently involved in poisonings. Specific antidotes such as receptor antagonists, chelating agents or specific antibodies are available for few poisons. General supportive and symptomatic treatment is all that can be done for others, and this is also important for poisons which have a selective antagonist.

The general detoxification and supportive measures are:

1. *Resuscitation and maintenance of vital functions*

a. Ensure patent airway, adequate ventilation,

give artificial respiration/100% oxygen inhalation as needed.

b. Maintain blood pressure and heart beat by fluid and crystalloid infusion, pressor agents, cardiac stimulants, pacing, defibrillation, etc, as needed.

c. Maintain body temperature.

d. Maintain blood sugar level by dextrose infusion, especially in patients with altered sensorium.

2. *Termination of exposure (decontamination)* by removing the patient to fresh air (for inhaled poisons), washing the skin and eyes (for poisons entering from the surface), induction of emesis with syrup ipecac or gastric lavage (for ingested poisons). Emesis should not be attempted in comatose or haemodynamically unstable patient, as well as for kerosene poisoning due to risk of aspiration into lungs. These procedures are also contraindicated in corrosive and CNS stimulant poisoning. Emesis/gastric lavage is not recommended if the patient presents > 2 hours after ingesting the poison; if the poison/its dose ingested are known to be non life-threatening, or if the patient has vomited after consuming the poison.

3. *Prevention of absorption of ingested poisons* A suspension of 20–40 g (1g/kg) of activated charcoal, which has large surface area and can adsorb many chemicals, should be administered in 200 ml of water. However, strong acids and alkalies, metallic salts, iodine, cyanide, caustics, alcohol, hydrocarbons and other organic solvents are not adsorbed by charcoal. Charcoal should not be administered if there is paralytic ileus or intestinal obstruction or when the patient reports > 2 hours after ingesting the poison.

4. *Hastening elimination* of the poison by inducing diuresis (furosemide, mannitol) or altering urinary pH (alkalinization for acidic drugs, e.g. barbiturates, aspirin). However, excretion of many poisons is not enhanced by forced diuresis and this procedure is generally not employed now. Haemodialysis and haemoperfusion (passage of blood through a column of charcoal or adsorbant resin) are more efficacious procedures.

4. Intolerance

It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses. It is the converse of tolerance and indicates a low threshold of the individual to the action of a drug. These are individuals who fall on the extreme left side of the Gaussian frequency distribution curve for sensitivity to the drug. Examples are:

- A single dose of triflupromazine induces muscular dystonias in some individuals, specially children.
- Only few doses of carbamazepine may cause ataxia in some people.
- One tablet of chloroquine may cause vomiting and abdominal pain in an occasional patient.

5. Idiosyncrasy

It is genetically determined abnormal reactivity to a chemical. The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction. As such, the type of reaction is restricted to individuals with a particular genotype (*see* p. 65). In addition, certain bizarre drug effects due to peculiarities of an individual (for which no definite genotype has been described) are included among idiosyncratic reactions, e.g.:

- Barbiturates cause excitement and mental confusion in some individuals.
- Quinine/quinidine cause cramps, diarrhoea, purpura, asthma and vascular collapse in some patients.
- Chloramphenicol produces nondose-related serious aplastic anaemia in rare individuals.

6. Drug allergy

It is an immunologically mediated reaction producing stereotype symptoms which are unrelated to the pharmacodynamic profile of the drug, generally occur even with much smaller doses and have a different time course of onset and

duration. This is also called *drug hypersensitivity*; but does not refer to increased response which is called supersensitivity. The target organs primarily affected in drug allergy are skin, airways, blood vessels, blood and gastrointestinal tract.

Allergic reactions occur only in a small proportion of the population exposed to the drug and cannot be produced in other individuals at any dose. Prior sensitization is needed and a latent period of at least 1–2 weeks is required after the first exposure. The drug or its metabolite acts as antigen (AG) or more commonly *hapten* (incomplete antigen: drugs have small molecules which become antigenic only after binding with an endogenous protein) and induce production of antibody (AB)/sensitized lymphocytes. Presence of AB to a drug is not necessarily followed by allergy to it. Chemically related drugs often show cross sensitivity. One drug can produce different types of allergic reactions in different individuals, while widely different drugs can produce the same reaction. The course of drug allergy is variable; an individual previously sensitive to a drug may subsequently tolerate it without a reaction and *vice versa*.

Cardinal features of drug allergy
• Manifestations unrelated to the pharmacodynamic actions of the drug.
• Manifestations similar to food/protein allergy, allergic diseases.
• Severity of reaction poorly correlated with dose of the drug; even small dose may trigger severe reaction.
• Occur only in few recipients, cannot be produced in other individuals.
• Prior sensitization (known/unknown) is needed.
• Positive dechallenge (on withdrawal of drug) and rechallenge (even with small dose).

Mechanism and types of allergic reactions

A. Humoral

Type-I (anaphylactic) reactions Reaginic antibodies (IgE) are produced which get fixed to the mast cells. On exposure to the drug, AG: AB reaction takes place on the mast cell surface (*see* Fig. 11.2) releasing mediators like histamine, 5-HT, leukotrienes (especially LT-C4 and D4), prostaglandins, PAF, etc. resulting in urticaria, itching, angioedema, bronchospasm, rhinitis or anaphylactic shock. Anaphylaxis is usually heralded by paresthesia, flushing, swelling of lips, generalized itching, wheezing, palpitation followed by syncope. The manifestations occur quickly after challenge and are called *immediate hypersensitivity*. Antihistaminic drugs are beneficial in some of these reactions.

Type-II (cytolytic) reactions Drug + component of a specific tissue cell act as AG. The resulting antibodies (IgG, IgM) bind to the target cells; on reexposure AG: AB reaction takes place on the surface of these cells, complement is activated and cytolysis occurs, e.g. thrombocytopenia, agranulocytosis, aplastic anaemia, haemolysis, organ damage (liver, kidney, muscle), systemic lupus erythematosus.

Type-III (retarded, Arthus) reactions These are mediated by circulating antibodies (predominantly IgG, mopping AB). AG: AB complexes bind complement and precipitate on vascular endothelium giving rise to a destructive inflammatory response. Manifestations are rashes, serum sickness (fever, arthralgia, lymphadenopathy), polyarteritis nodosa, Stevens-Johnson syndrome (erythema multiforme, arthritis, nephritis, myocarditis, mental symptoms). The reaction usually subsides in 1–2 weeks.

B. Cell mediated

Type-IV (delayed hypersensitivity) reactions These are mediated through production of sensitized T-lymphocytes carrying receptors for the AG. On contact with the AG these T cells produce *lymphokines* which attract granulocytes and generate an inflammatory response, e.g. contact dermatitis, some rashes, fever, photosensitization. The reaction generally takes > 12 hours to develop.

Treatment of drug allergy
The offending drug must be immediately stopped. Most mild reactions (like skin rashes) subside

by themselves and donot require specific treatment. Antihistamines (H_1) are beneficial in some type I reactions (urticaria, rhinitis, swelling of lips, etc.) and some skin rashes (*see* p. 167). In case of anaphylactic shock or angioedema of larynx the resuscitation council of UK has recommended the following measures:

- Put the patient in reclining position, administer oxygen at high flow rate and perform cardiopulmonary resuscitation if required.
- Inject adrenaline 0.5 mg (0.5 ml of 1 in 1000 solution for adult, 0.3 ml for child 6-12 years and 0.15 ml for child upto 6 years) i.m.; repeat every 5–10 min in case patient does not improve or improvement is transient. This is the only life saving measure. Adrenaline should not be injected i.v. (can itself be fatal) unless shock is immediately life threatening. If adrenaline is to be injected i.v., it should be diluted to 1:10,000 or 1:100,000 and infused slowly with constant monitoring.
- Administer a H_1 antihistaminic (chlorpheniramine 10–20 mg) i.m./slow i.v. It may have adjuvant value.
- Intravenous glucocorticoid (hydrocortisone sod. succinate 200 mg) should be added in severe/recurrent cases. It acts slowly, but is specially valuable for prolonged reactions and in asthmatics. It may be followed by oral prednisolone for 3 days.

Adrenaline followed by a short course of glucocorticoids is indicated for bronchospasm attending drug hypersensitivity. Glucocorticoids are the only drug effective in type II, type III and type IV reactions.

Skin tests (intradermal, patch) or intranasal tests may forewarn in case of Type I hypersensitivity, but not in case of other types. However, these tests are not entirely reliable—false positive and false negative results are not rare.

7. Photosensitivity

It is a cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. The reactions are of two types:

(a) Phototoxic Drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction followed by a photobiological reaction resulting in local tissue damage (sunburn-like), i.e. erythema, edema, blistering which have fast onset and shorter duration after exposure ends. This is followed by hyperpigmentation and desquamation. The lesions may be more severe with larger doses of the drug. The shorter wave lengths (290–320 nm, UV-B) are responsible. Drugs involved in acute phototoxic reactions are tetracyclines (especially demeclocycline) and tar products. Drugs causing chronic and low grade sensitization are nalidixic acid, fluoroquinolones, dapsone, sulfonamides, phenothiazines, thiazides, amiodarone. This type of reaction is more common than photoallergic reaction.

(b) Photoallergic Drug or its metabolite induces a cell mediated immune response which on exposure to light of longer wave lengths (320–400 nm, UV-A) produces a papular or eczematous contact dermatitis like picture that may persist long after exposure. Rarely antibodies mediate photoallergy and the reaction takes the form of immediate flare, itching and wheal on exposure to sun. Even small doses may trigger the reaction and lesions may extend beyond the exposed area. Drugs involved are sulfonamides, sulfonylureas, griseofulvin, chloroquine, chlorpromazine, carbamazepine.

8. Drug dependence

Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, recreation, withdrawal from reality, social adjustment, etc. Drug dependence is a state in which use of drugs for personal satisfaction is accorded a higher priority than other basic needs, often in the face of known risks to health.

Drugs frequently causing allergic reactions	
Penicillins	Salicylates
Cephalosporins	Carbamazepine
Sulfonamides	Allopurinol
Tetracyclines	ACE inhibitors
Quinolones	Methyldopa
Antitubercular drugs	Hydralazine
Phenothiazines	Local anaesthetics

There is a lot of confusion in terminology and definitions; the following may serve to describe different aspects of the problem.

Psychological dependence   It is said to have developed when the individual believes that optimal state of wellbeing is achieved only through the actions of the drug. The subject feels emotionally distressed if the drug is not taken. It may start as liking for the drug effects and may progress to compulsive drug use in some individuals who then lose control over the use of the drug. The intensity of psychological dependence may vary from *desire* to *craving*. Obviously, certain degree of psychological dependence accompanies all patterns of self medication.

Reinforcement   is the ability of the drug to produce effects that the user enjoys and which make him/her wish to take it again or to induce *drug seeking behaviour*. Certain drugs (opioids, cocaine) are strong reinforcers, while others (benzodiazepines) are weak reinforcers. Faster the drug acts, more reinforcing it is. Thus, inhaled drugs and those injected i.v. are highly reinforcing—produce an intense 'high' in dependent individuals.

Physical dependence   It is an altered physio-logical state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic *withdrawal (abstinence) syn-drome*. Since the essence of the process is adaptation of the nervous system to function normally in the presence of the drug, it has been called *'neuroadaptation'*.

Drugs producing physical dependence are—opioids, barbiturates and other depressants inc-luding alcohol and benzodiazepines. Stimulant drugs, e.g. amphetamines, cocaine produce little or no physical dependence.

Drug abuse   Refers to use of a drug by self-medication in a manner and amount that deviates from the approved medical and social patterns in a given culture at a given time. The term conveys

social disapproval of the manner and purpose of drug use. For regulatory agencies, *drug abuse* refers to any use of an ilicit drug.

The two major patterns of drug abuse are:
a. *Continuous use:* The drug is taken regularly, the subject wishes to continuously remain under the influence of the drug, e.g. opioids, alcohol, sedatives.
b. *Occasional use:* The drug is taken off and on to obtain pleasure or high, recreation (as in rave parties) or enhancement of sexual experience, e.g. cocaine, amphetamines, psy-chedelics, binge drinking (alcohol), cannabis, solvents (inhalation), etc.

Drug addiction   It is a pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug. Procuring the drug and using it takes precedence over other activities. Even after withdrawal most addicts tend to relapse. Physical dependence, though a strong impetus for continued drug use, is not an essential feature of addiction. Amphetamines, cocaine, cannabis, LSD are drugs which produce addiction but little/no physical dependence. On the other hand, drugs like nalorphine produce physical dependence without imparting addiction in the sense that there is little drug seeking behaviour.

Drug habituation   It denotes less intensive involvement with the drug, so that its withdrawal produces only mild discomfort. Consumption of tea, coffee, tobacco, social drinking are regarded habituating, physical dependence is absent.

Basically, habituation and addiction imply different degrees of psychological dependence and it may be difficult to draw a clearcut line of distinction between the two. Therefore, it is better to avoid using these terms in describing drug dependence and related conditions.

9. Drug withdrawal reactions

Apart from drugs that are usually recognised as producing dependence, sudden interruption of therapy with certain other drugs also results in adverse consequences, mostly in the form of

worsening of the clinical condition for which the drug was being used, e.g.:

  (i) Acute adrenal insufficiency may be precipitated by abrupt cessation of corticosteroid therapy.

  (ii) Severe hypertension, restlessness and sympathetic overactivity may occur shortly after discontinuing clonidine.

  (iii) Worsening of angina pectoris, precipitation of myocardial infarction may result from stoppage of β blockers.

  (iv) Frequency of seizures may increase on sudden withdrawal of an antiepileptic.

These manifestations are also due to adaptive changes and can be minimized by gradual withdrawal.

10. Teratogenicity

It refers to the capacity of a drug to cause foetal abnormalities when administered to the pregnant mother. The placenta does not constitute a strict barrier, and any drug can cross it to a greater or lesser extent. The embryo is one of the most dynamic biological systems and in contrast to adults, drug effects are often irreversible. The thalidomide disaster (1958–61) resulting in thousands of babies born with *phocomelia* (seal like limbs) and other defects focused attention onto this type of adverse effect.

Drugs can affect the foetus at 3 stages—

  (i) *Fertilization and implantation*—conception to 17 days—failure of pregnancy which often goes unnoticed.

  (ii) *Organogenesis*—18 to 55 days of gestation—most vulnerable period, deformities are produced.

  (iii) *Growth and development*—56 days onwards — developmental and functional abnormalities can occur, e.g. ACE inhibitors can cause hypoplasia of organs, especially of lungs and kidneys; NSAIDs may induce premature closure of ductus arteriosus; androgens and progestins cause masculanization of female foetus, antithyroid drugs and lithium cause foetal goiter.

The type of malformation depends on the drug as well as the stage at which exposure to the teratogen occurred. Foetal exposure depends on the blood level and duration for which the drug remains in maternal circulation. The teratogenic potential of a drug is to be considered against the background of congenital abnormalities occurring spontaneously, which is ~ 2% of all pregnancies. Majority of implicated drugs are low

Human teratogenic drugs	
Drug	*Abnormality*
Thalidomide	phocomelia, multiple defects of internal organs
Anticancer drugs (methotrexate)	cleft palate, hydrocephalus, multiple defects, foetal death
Androgens	virilization; limb, esophageal, cardiac defects
Progestins	virilization of female foetus
Stilboestrol	vaginal carcinoma in teenage female offspring
Tetracyclines	discoloured and deformed teeth, retarded bone growth
Warfarin	depressed nose; eye and hand defects, growth retardation
Phenytoin	hypoplastic phalanges, cleft lip/palate, microcephaly
Phenobarbitone	various malformations
Carbamazepine	neural tube defects, assorted abnormalities
Valproate sod.	spina bifida and other neural tube defects, heart and limb abnormalities
Alcohol	low IQ baby, growth retardation, foetal alcohol syndrome
ACE inhibitors	hypoplasia of organs, growth retardation, foetal loss
Lithium	foetal goiter, cardiac and other abnormalities
Antithyroid drugs	foetal goiter and hypothyroidism
Indomethacin/aspirin	premature closure of ductus arteriosus
Isotretinoin	craniofacial, heart and CNS defects, hydrocephalus

Risk category of drugs during pregnancy*		
Category		*Examples*
A No risk	Adequate studies in pregnant women have failed to demonstrate a risk to the foetus	Inj. Mag. sulfate, thyroxine
B No evidence of risk in humans	Adequate human studies are lacking, but animal studies have failed to demonstrate a risk to the foetus or Adequate studies in pregnant women have failed to demonstrate a risk to the foetus, but animal studies have shown an adverse effect on the foetus	Penicillin V, amoxicillin, cefactor, erythromycin, paracetamol, lidocaine
C Risk cannot be ruled old	No adequate studies in pregnant women, and animal studies are lacking or have shown an adverse effect on foetus, but potential benefit may warrant use of the drug in pregnant women despite potential risk	Morphine, codeine, atropine, corticosteroids, adrenaline, thiopentone, bupivacaine
D Benefit may out weigh potential risk	There is evidence of human foetal risk, but the potential benefits from use of the drug may be acceptable despite the potential risk	Aspirin, phenytoin, carbamazepine, valproate, lorazepam, methotrexate
X Contra-indicated	Studies in animals or humans have demonstrated foetal abnormalities, and potential risk clearly outweighs possible benefit	Estrogens, isotretinoin, ergometrine thalidomide

* As per US-FDA.

grade teratogens, i.e. increase the incidence of malformations only slightly, which may be very difficult to detect, confirm or refute. Nevertheless, some drugs have been clearly associated with causing foetal abnormalities in human beings. These are listed in the box. However, only few mothers out of all those who receive these drugs during the vulnerable period will get a deformed baby, but the exact risk posed by a drug is difficult to estimate.

The US-FDA has graded the documentation of risk for causing birth defects into five categories (*see* box).

It is, therefore, wise to avoid all drugs during pregnancy unless compelling reasons exist for their use regardless of the assigned pregnancy category, or presumed safety (also *see* Appendix-3).

Frequency of spontaneous as well as drug induced malformations, especially neural tube defects, may be reduced by folate therapy during pregnancy.

11. Mutagenicity and Carcinogenicity

It refers to capacity of a drug to cause genetic defects and cancer respectively. Usually oxidation of the drug results in the production of reactive intermediates which affect genes and may cause structural changes in the chromosomes. Covalent interaction with DNA can modify it to induce mutations, which may manifest as heritable defects in the next generation. If the modified DNA sequences code for factors that regulate cell proliferation/growth, i.e. are protooncogenes, or for

CHAPTER 6

proteins that inhibit transcription of protoon-cogenes, a tumour (cancer) may be produced. Even without interacting directly with DNA, certain chemicals can promote malignant change in genetically damaged cells, resulting in carcino-genesis. Chemical carcinogenesis generally takes several (10–40) years to develop. Drugs implicated in these adverse effects are—anticancer drugs, radioisotopes, estrogens, tobacco. Generally, drugs which show mutagenic or carcinogenic potential are not approved for marketing/are withdrawn, unless they are useful in life-threatening conditions.

12. Drug induced diseases

These are also called *iatrogenic* (physician indu-ced) diseases, and are functional disturbances (disease) caused by drugs which persist even after the offending drug has been withdrawn and largely eliminated, e.g.:

Peptic ulcer by salicylates and corticosteroids.
Parkinsonism by phenothiazines and other antipsychotics.
Hepatitis by isoniazid.
DLE by hydralazine.

☞ PROBLEM DIRECTED STUDY

6.1 A 40-year-man weighing 60 kg suffering from chronic cough with expectoration and fever was diagnosed to have cavitary pulmonary tuberculosis. He was put on the standard 1st line antitubercular regimen consisting of isoniazid (H) + rifampin (R) + pyrazinamide (Z) + ethambutol (E). His condition improved, but in the 4th week he developed jaundice with enlarged tender liver and rise in serum bilirubin as well as serum transaminase levels. He was suspected to have developed antitubercular drug induced hepatitis.

(a) Should his antitubercular treatment be stopped or continued?

(b) How would you proceed to confirm and identify the causative drug, and then select the alternative regimen?

(see Appendix-1 for solution)

DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM

Chapter 7a   Autonomic Nervous System: General Considerations

ORGANIZATION AND FUNCTION

The autonomic nervous system (ANS) functions largely below the level of consciousness and controls visceral functions. The major differences between the somatic and autonomic nervous systems are given in Table II.1.

Like the somatic nervous system, the ANS consists of afferents, centre and efferents.

Autonomic afferents   Most visceral nerves are mixed nerves and carry nonmyelinated visceral afferent fibres as well. The cell bodies of these afferent fibres are located in the dorsal root ganglion of spinal nerves and in the sensory ganglia (e.g. nodose ganglion of vagus) of cranial nerves. They mediate visceral pain as well as cardiovascular, respiratory and other visceral reflexes.

Central autonomic connections   There are no exclusively autonomic areas in the CNS; considerable intermixing and integration of somatic and autonomic innervation occurs. The highest seat regulating autonomic functions is in the hypothalamus—posterior and lateral nuclei are primarily sympathetic while anterior and medial nuclei are primarily parasympathetic. Many autonomic centres (pupillary, vagal, respiratory, etc.) are located in the mid-brain and the medulla in relation to the cranial nerves. The lateral column in the thoracic spinal cord contains cells which give rise to the sympathetic outflow.

Autonomic efferents   The motor limb of the ANS is anatomically divided into sympathetic and parasympathetic. Many organs receive both sympathetic and parasympathetic innervation and

TABLE II.1	Differences between somatic and autonomic nervous system		
		Somatic	*Autonomic*
1.	Organ supplied	Skeletal muscles	All other organs
2.	Distal most synapse	Within CNS	Outside CNS (in ganglia)
3.	Nerve fibres	Myelinated	Pregang.—myelinated Postgang.—non-myelinated
4.	Peripheral plexus formation	Absent	Present
5.	Primary efferent transmitter	Acetylcholine	Acetylcholine, Noradrenaline
6.	Effect of nerve section on organ supplied	Paralysis and atrophy	Activity maintained, no atrophy

the two subdivisions are functionally antagonistic in majority of these. The level of activity of innervated organ at a given moment is the algebraic sum of sympathetic and parasympathetic tone. However, refractory period of atrial fibres is decreased by sympathetic as well as parasympathetic influences. Most blood vessels, spleen, sweat glands and hair follicles receive only sympathetic, while ciliary muscle, bronchial smooth muscle, gastric and pancreatic glands receive only parasympathetic innervation. Thus, the two divisions of ANS are not merely check-and-balance physiological antagonists of each other.

Enteric nervous system

The enteric plexus of nerves receives inputs from both sympathetic and parasympathetic divisions of ANS, but in addition functions independently to integrate bowel movements as well as regulate secretion and absorption (*see* Fig. 47.2). As such, it has also been labelled as a distinct *'enteric nervous system'*.

The general layout of ANS is depicted in Fig. II.1 and the important differences between its two subdivisions are given in Table II.2.

NEUROHUMORAL TRANSMISSION

Neurohumoral transmission implies that nerves transmit their message across synapses and neuroeffector junctions by the release of humoral (chemical) messengers.

Junctional transmission was thought to be electrical (it does occur in some lower animals and probably in certain areas of mammalian brain) but observations at the turn of last century prompted Elliott (1905) to suggest that
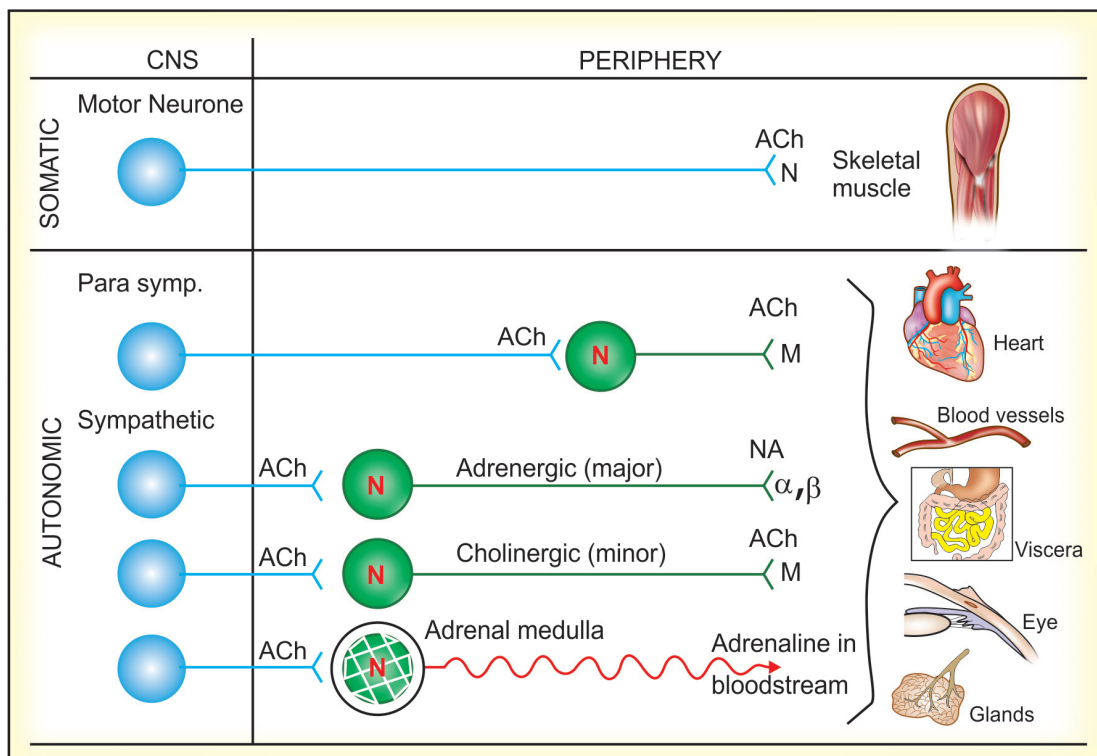
Fig. II.1: The general outlay of efferent autonomic nervous system. The transmitter released and the primary postjunctional receptor subtype is shown at each synapse/neuroeffector junction
ACh= Acetylcholine, NA= Noradrenaline, N = Nicotinic,   M = Muscarinic, α = α adrenergic, β = β adrenergic

SECTION 2

TABLE II.2	Differences between sympathetic and parasympathetic divisions of the autonomic nervous system	
	Sympathetic	*Parasympathetic*
1. Origin	Dorso-lumbar (T_1 to L_2 or L_3)	Cranio-sacral (III, VII, IX, X; S_2–S_4)
2. Distribution	Wide	Limited to head, neck and trunk
3. Ganglia	Away from the organs supplied	On or close to the organ supplied
4. Postgang. fibre	Long	Short
5. Pre: post ganglionic fibre ratio	1: 20 to 1: 100	1: 1 to 1: 2 (except in enteric plexuses)
6. Neuroeffector transmitter	Major: NA Minor: ATP, NPY, DA, ACh	Major: ACh Minor: VIP, NO
7. Stability of transmitter	NA stable, diffuses for wider actions	ACh—rapidly destroyed locally
8. Important function	Tackling stress and emergency	Assimilation of food, conservation of energy

NA—Noradrenaline, ACh—Acetylcholine, ATP—Adenosine triphosphate, NPY—Neuropeptide Y, DA—Dopamine, VIP—Vasoactive intestinal peptide, NO—Nitric oxide

sympathetic nerves functioned by the release of an adrenaline-like substance, and Dixon (1907) to propose that vagus released a muscarine like chemical. Otto Loewi (1921) provided direct proof of humoral transmission by perfusing two frog hearts in series. Stimulation of vagus nerve of the first heart caused arrest of both. Thus, a chemical must have been released by vagal stimulation in the first heart which passed in the perfusate and arrested the second heart. This *vagusstoff* was found in 1926 to be acetylcholine, which earlier Dale (1914) had characterised as 'parasympathomimetic'. The sympathetic transmitter was eventually shown to be noradrenaline in 1946 by Von Euler. Many humoral transmitters (dopamine, 5-HT, GABA, glutamic acid, purines, peptides, etc.) are now known.

To be considered as a postjunctionally acting neurohumoral transmitter a substance must fulfill the following criteria:

(i) It should be present in the presynaptic neurone (usually along with enzymes synthesizing it).

(ii) It should be released in the medium following nerve stimulation.

(iii) Its application should produce responses identical to those produced by nerve stimulation.

(iv) Its effects should be antagonized or potentiated by other substances which similarly alter effects of nerve stimulation.

Steps in neurohumoral transmission

I. Impulse conduction The resting transmembrane potential (70 mV negative inside) is established by high K^+ permeability of axonal membrane and high axoplasmic concentration of this ion coupled with low Na^+ permeability and its active extrusion from the neurone. Stimulation or arrival of an electrical impulse causes a sudden increase in Na^+ conductance → depolarization and overshoot (reverse polarization: inside becoming 20 mV positive); K^+ ions then move out in the direction of their concentration gradient and repolarization is achieved. The ionic distribution is normalized during the refractory period by the activation of Na^+ K^+ pump. The action potential (AP) thus generated sets up local circuit currents which activate ionic channels at the next excitable part of the membrane (next node of Ranvier in myelinated fibre) and the AP is propagated without decrement.

Tetrodotoxin (from puffer fish) and saxitoxin (from certain shell-fish) selectively abolish increase in Na^+ conductance in nerve fibres and thus block impulse conduction.

II. Transmitter release The transmitter (excitatory or inhibitory) is stored in prejunctional nerve endings within 'synaptic vesicles' (Fig. II.2). Nerve impulse promotes fusion of vesicular and axonal membranes through Ca^{2+}
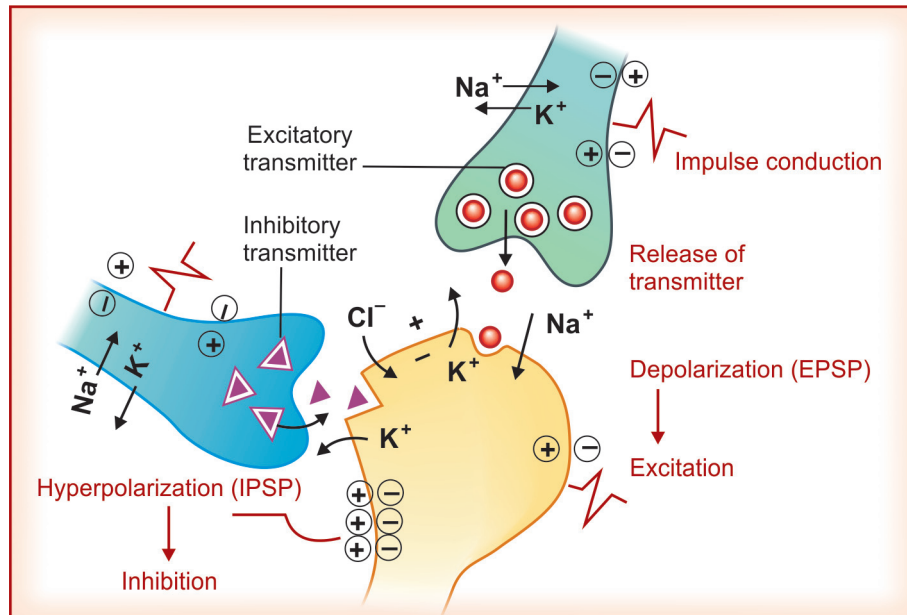
Fig. II.2: Diagrammatic representation of steps in excitatory and inhibitory neurohumoral transmission: EPSP = Excitatory postsynaptic potential; IPSP = Inhibitory postsynaptic potential

entry which fluidizes membranes. All contents of the vesicle (transmitter, enzymes and other proteins) are extruded (exocytosis) in the junctional cleft.

A number of proteins like synaptotagmin, synaptobrevin, neurexin, syntaxin and synaptophysin located on the vesicular and axonal membranes have been found to participate in the docking and fusion of the synaptic vesicles with the axonal membrane resulting in exocytosis. These proteins can be targets of drug action to modify junctional transmission.

While majority of the neurotransmitters are preformed, kept stored in synaptic vesicles and released on activation by exocytosis as outlined above, some mediators like NO, prostaglandins, endocannabinoids are synthesized on demand and reach their target by diffusion or by active transport.

The release process can be modulated by the transmitter itself and by other agents through activation of specific receptors located on the prejunctional membrane, e.g. noradrenaline (NA) release is inhibited by NA (α_2 receptor), dopamine, adenosine, prostaglandins and enkephalins while isoprenaline (β_2 receptor) and angiotensin (AT$_1$ receptor) increase NA release. Similarly, α_2 and muscarinic agonists inhibit acetylcholine (ACh) release at autonomic neuroeffector sites (but not in ganglia and skeletal muscles).

III. Transmitter action on postjunctional membrane The released transmitter combines with specific receptors on the postjunctional membrane and depending on its nature induces an excitatory postsynaptic potential (EPSP) or an inhibitory postsynaptic potential (IPSP).

EPSP Increase in permeability to cations → Na$^+$ or Ca^{2+} influx (through fast or slow channels) causes *depolarization* followed by K$^+$ efflux. These ionic movements are passive as the flow is down the concentration gradients.

IPSP Increase in permeability to anions, so that Cl$^-$ ions move in (axonal Cl$^-$ concentration is lower than its extracellular concentration) and tend to hyperpolarize the membrane → an IPSP is generated. Stabilization of the membrane or hyperpolarization can also result from selective
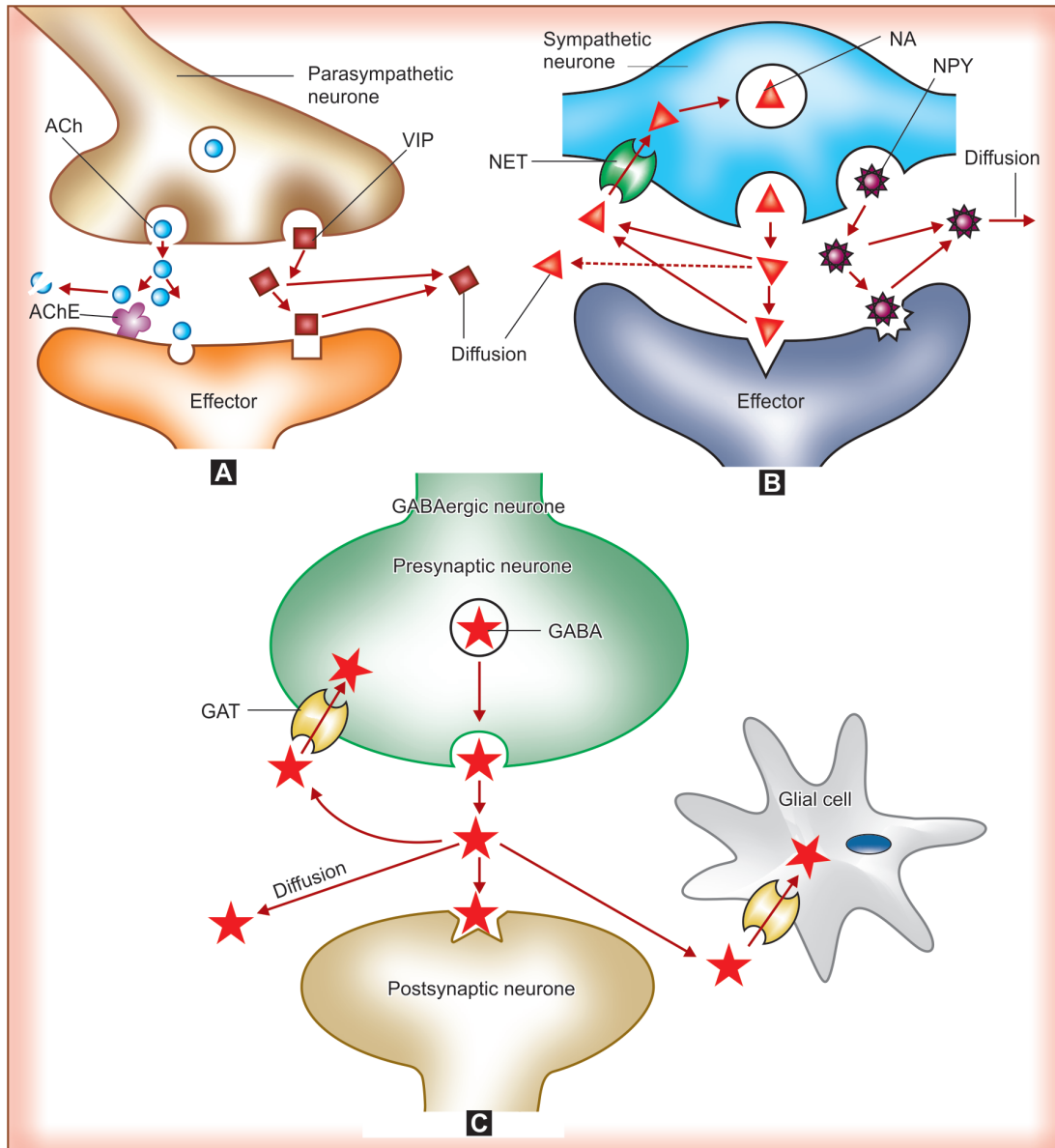
Fig. II.3: Mechanisms of termination of transmitter action

A. Parasympathetic neurone: The primary transmitter acetylcholine (ACh) is rapidly hydrolysed by a specific enzyme acetylcholinesterase (AChE) located strategically on the synaptic membrane. A common co-transmitter is vasoactive intestinal peptide (VIP), which on release diffuses slowly to be degraded by peptidases at distant sites. It may act on the same as well as neighbouring effectors.

B. Sympathetic neurone: The primary transmitter noradrenaline (NA) is largely taken back into the neurone by membrane-bound norepinephrine transporter (NET) and recycled. A minor fraction diffuses away. One of the cotransmitters is neuropeptide Y (NPY), which on release meets the same fate as VIP.

C. Gabaergic neurone: The amino acid transmitter gamma-aminobutyric acid (GABA) released into the synaptic cleft is partly taken up into the neurone by GABA transporter (GAT), as well as into neighbouring glial cells. Some of it dissipates by diffusion.

increase in permeability to K^+ ions, which move out carrying +ive charges.

In addition, a trophic influence on junctional morphology and functional status is exerted by the background basal release of the transmitter.

IV. Postjunctional activity A suprathreshold EPSP generates a propagated postjunctional AP which results in nerve impulse (in neurone), contraction (in muscle) or secretion (in gland). An IPSP stabilizes the postjunctional membrane and resists depolarizing stimuli.

V. Termination of transmitter action The various mechanisms of termination of transmitter action are depicted in Fig. II.3. Following its combination with the receptor, the transmitter is either locally degraded (e.g. ACh) or is partly taken back into the prejunctional neurone by active reuptake and partly diffuses away (e.g. NA). Specific carrier proteins like norepinephrine transporter (NET), dopamine transporter (DAT), serotonin transporter (SERT) are expressed on the axonal membrane for this purpose. The rate of termination of transmitter action governs the rate at which responses can be transmitted across a junction (1 to 1000/sec).

Aminoacid transmitters (glutamate, GABA) are also partly taken up by active transport into neuronal and neighbouring glial cells, but no active reuptake of peptide neurotransmitters (VIP, NPY, enkephalins, etc.) occurs. They diffuse away and are broken down by peptidases at distant sites.

Cotransmission

It has now become apparent that the classical 'one neurone—one transmitter' model is an over simplification. Most peripheral and central neurones on stimulation have been shown to release more than one active substance. In the ANS, besides the primary transmitters ACh and NA, neurones have been found to elaborate purines (ATP, adenosine), peptides (vasoactive intestinal peptide or VIP, neuropeptide-Y or NPY, substance P, enkephalins, somatostatin, etc.), nitric oxide (NO) and prostaglandins as co-
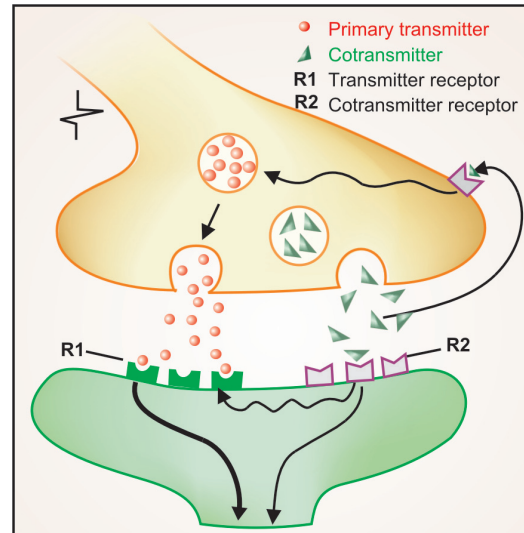

Fig. II.4: Cotransmission
The cotransmitter is stored in the prejunctional nerve terminal alongwith the primary transmitter, but in separate vesicles (in some cases in the same vesicle itself). Nerve impulse releases both the transmitters concurrently. Acting on its own receptors, the cotransmitter modifies responsiveness of the effector to the primary transmitter or substitutes for it. Cotransmitter may also act on prejunctional receptors and modulate release of the transmitters

transmitters. In most autonomic cholinergic neurones VIP is associated with ACh, while ATP is associated with both ACh and NA. The transmitter at some parasympathetic sites is NO, and these are called *nitrergic nerves*. Vascular adrenergic nerves contain NPY which causes long lasting vasoconstriction. The cotransmitter is stored in the same neurone but in distinct synaptic vesicles or locations (Fig. II.4). However, ATP is stored with NA in the same vesicle. On being released by nerve impulse the contransmitter may serve to regulate the presynaptic release of the primary transmitter and/or postsynaptic sensitivity to it (neuromodulator role). The cotransmitter may also serve as an alternative transmitter in its own right and/or exert a trophic influence on the synaptic structures.

Nonadrenergic, noncholinergic (NANC) transmission has been demonstrated in the autonomic innervation of the gut, vas deferens,

urinary tract, salivary glands and certain blood vessels, where nerve stimulation is able to evoke limited responses even in the presence of total adrenergic and cholinergic blockade. For example, it has been shown that stimulation of sympathetic nerve to guinea pig vas deferens elicits a biphasic contractile response, the initial short-lasting phase of which is mediated by ATP (through P2 receptors) and the second longer lasting phase by NA (through α_1 receptors).

The time-course of action of the primary transmitter and the cotransmitter is usually different. The cotransmitter VIP of parasympathetic neurones produces a slow and long-lasting response, while another one (NO) has an intermediate time-course of action between VIP and ACh (fast acting). Similarly, in sympathetic neurones, the cotransmitter NPY is slower acting and ATP faster acting than NA. Moreover, cotransmitters like NO, VIP, NPY diffuse to a wider area, and can affect receptors at some distance from the site of release.

Many anomalous findings have been explained by the revelation of cotransmission.
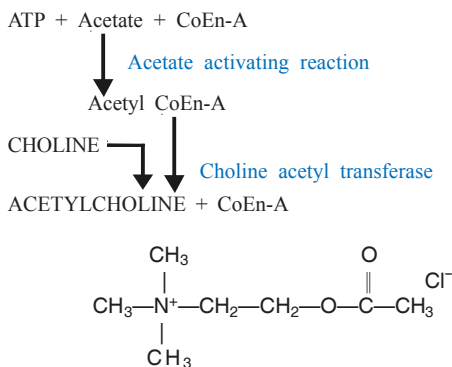
Chapter 7b Cholinergic System and Drugs

CHOLINERGIC TRANSMISSION

Acetylcholine (ACh) is a major neurohumoral transmitter at autonomic, somatic as well as central sites. These sites are listed in Table 7.1

Synthesis, storage and destruction of ACh

The cholinergic neuronal mechanisms are summarized in Fig. 7.1.

Acetylcholine is synthesized locally in the cholinergic nerve endings by the following pathway—

ATP + Acetate + CoEn-A

Acetate activating reaction

Acetyl CoEn-A

CHOLINE

Choline acetyl transferase

ACETYLCHOLINE + CoEn-A

$$CH_3-N^+-CH_2-CH_2-O-C-CH_3 \quad Cl^-$$

ACETYLCHOLINE CHLORIDE

Choline is actively taken up by the axonal membrane by a Na^+: choline cotransporter and acetylated with the help of ATP and coenzyme-A by the enzyme *choline acetyl transferase* present in the axoplasm. *Hemicholinium* (HC3) blocks choline uptake (the rate limiting step in ACh synthesis) and depletes ACh. Most of the ACh is stored in ionic solution within small synaptic vesicles, but some free ACh is also present in the cytoplasm of cholinergic terminals. Active transport of ACh into synaptic vesicles is effected by another carrier which is blocked by *vesamicol*.

Release of ACh from nerve terminals occurs in small quanta—amount contained in individual vesicles is extruded by exocytosis. In response to a nerve AP synchronous release of multiple quanta triggers postjunctional events.

Two toxins interfere with cholinergic transmission by affecting release: *botulinum toxin* inhibits release, while *black widow spider toxin* induces massive release and depletion.

Botulinum toxin

Botulinum toxin A and B are highly potent exotoxins produced by *Clostridium botulinum* that are responsible for 'botulism' (a type of food poisoning). These neurotoxic proteins cause long-lasting loss of cholinergic transmission by interacting with axonal proteins involved in exocytotic release of ACh. Localized injection of minute quantity of botulinum toxin A (BOTOX) or its haemagglutinin complex (DYSPORT) can be used in the treatment of a number of spastic and other neurological conditions due to overactivity of cholinergic nerves, like blepharospasm, spastic cerebral palsy, strabismus, spasmodic torticollis, nystagmus, hemifacial spasm, post stroke spasticity, spasmodic dysphonia, axillary hyperhydrosis, etc. It is increasing being employed as beauty treatment by removal of age-related facial wrinkles. However, its incorrect injection or overdose can be dangerous; ptosis, diplopia, facial swelling, dry mouth, dysphagia, dysarthria, muscular weakness and even respiratory paralysis has occurred.

Cholinesterase Immediately after release, ACh is hydrolyzed by the enzyme cholinesterase and choline is recycled. A specific (*Acetylcholinesterase*—AChE or true cholinesterase) and a nonspecific (*Butyrylcholinesterase*—BuChE or pseudocholinesterase) type of enzyme occurs in the body; important differences between these two types of the enzyme are given in Table 7.2. While AChE is strategically located at all cholinergic sites and serves to inactivate ACh instantaneously, BuChE present in plasma and elsewhere probably serves to metabolize ingested esters.
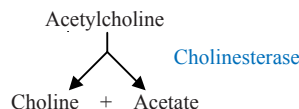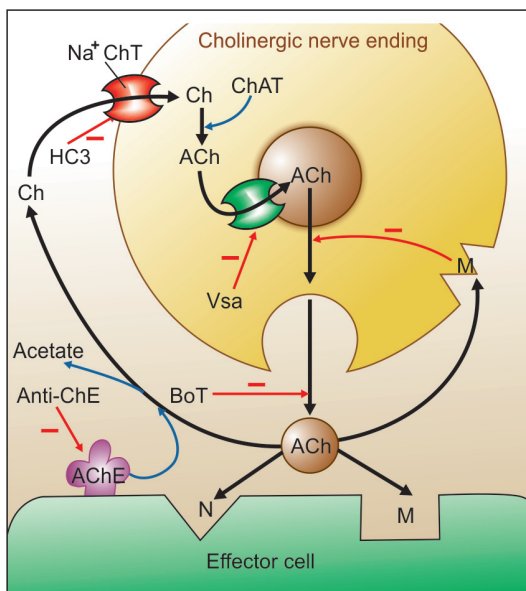
Acetylcholine

Cholinesterase

Choline + Acetate

TABLE 7.1	Sites of cholinergic transmission and type of receptor involved			
	Site	*Type of receptor*	*Selective agonist*	*Selective antagonist*
1.	*a.* All postganglionic parasymp. *b.* Few postganglionic symp. (sweat glands, some blood vessels)	Muscarinic	Muscarine	Atropine
2.	*a.* Ganglia (both symp. and parasymp). *b.* Adrenal medulla	Nicotinic (N_N)	DMPP*	Hexamethonium
3.	Skeletal muscles	Nicotinic (N_M)	PTMA**	d-tubocurarine
4.	CNS (cortex, basal ganglia, spinal cord and other sites)	Muscarinic	Muscarine/ Oxotremorine	Atropine
		Nicotinic	Carbachol	d-tubocurarine

*   DMPP—Dimethyl phenyl piperazinium
** PTMA—Phenyl trimethyl ammonium

Fig. 7.1: Cholinergic neuronal mechanisms
Minus sign indicates inhibition while bold blue arrow indicates active transport
Ch—Choline, ACh—Acetylcholine, ChAT—Choline acetyl transferase, AChE—Acetylcholinesterase, Anti-ChE—Anticholinesterase, M—Muscarinic receptor, N—Nicotinic receptor, HC3—Hemicholinium, BoT—Botulinum toxin, Vsa—Vesamicol, Na⁺ChT—Na⁺–Choline Cotransporter.

Cholinoceptors

Two classes of receptors for ACh are recognised —muscarinic and nicotinic; the former is a G protein coupled receptor, while the latter is a ligand gated cation channel.

Muscarinic   These receptors are selectively stimulated by muscarine and blocked by atropine. They are located primarily on autonomic effector cells in heart, blood vessels, eye, smooth muscles and glands of gastrointestinal, respiratory and urinary tracts, sweat glands, etc. and in the CNS. Subsidiary muscarinic receptors are also present in autonomic ganglia where they appear to play a modulatory role by inducing a long-lasting late EPSP.

Muscarinic autoreceptors are present prejunctionally on post-ganglionic cholinergic nerve endings: their activation inhibits further ACh release. Similar ones have been demonstrated on adrenergic terminals: their activation inhibits NA release (may contribute to vasodilator action of injected ACh). All blood vessels have muscarinic receptors (though most of them lack cholinergic innervation) located on endothelial cells whose activation releases EDRF (nitric oxide) which diffuses to the smooth muscle to cause relaxation.

Subtypes of muscarinic receptor   By pharmacological as well as molecular cloning techniques, muscarinic receptors have been divided into 5 subtypes M_1, M_2, M_3, M_4 and M_5. The first 3 are the major subtypes (Table 7.3) that are present on effector cells as well as on prejunctional nerve endings, and are expressed both in peripheral organs as well as in the CNS. The M_4 and M_5 receptors are present mainly on nerve endings in certain areas of the brain and regulate the release of other neurotransmitters. Functionally, M_1, M_3

TABLE 7.2	Differences between the two types of cholinesterases	
	Acetylcholinesterase (True)	*Butyrylcholinesterase (Pseudo)*
1. Distribution	All cholinergic sites, RBC, gray matter	Plasma, liver, intestine, white matter
2. Hydrolysis		
ACh	Very fast (in μs)	Slow
Methacholine	Slower than ACh	Not hydrolysed
Benzoylcholine	Not hydrolysed	Hydrolysed
Butyrylcholine	Not hydrolysed	Hydrolysed
3. Inhibition	More sensitive to physostigmine	More sensitive to organophosphates
4. Function	Termination of ACh action	Hydrolysis of ingested esters

and M_5 fall in one class while M_2 and M_4 fall in another class. Muscarinic agonists have shown little subtype selectivity, but some relatively selective antagonists have been produced (pirenzepine for M_1, tripitramine for M_2 and darifenacin for M_3). Most organs have more than one subtype, but usually one subtype predominates in a given tissue.

M_1: The M_1 is primarily a neuronal receptor located on ganglion cells and central neurones, especially in cortex, hippocampus and corpus striatum. It plays a major role in mediating gastric secretion, relaxation of lower esophageal sphincter (LES) caused by vagal stimulation, and in learning, memory, motor functions, etc.

M_2: Cardiac muscarinic receptors are predominantly M_2 and mediate vagal bradycardia. Autoreceptors on cholinergic nerve endings are also of M_2 subtype. Smooth muscles express some M_2

TABLE 7.3	Characteristics of important subtypes of muscarinic receptor		
	M_1	*M_2*	*M_3*
1. Location and function subserved	*Autonomic ganglia:* Depolarization (late EPSP) *Gastric glands:* Hist. release, acid secretion *CNS:* Learning, memory, motor functions	*SA node:* Hyperpolarization, ↓ rate of impulse generation *AV node:* ↓ velocity of conduction *Atrium:* shortening of APD, ↓ contractility *Ventricle:* ↓ contractility (slight) (receptors sparse) *Cholinergic nerve endings:* ↓ ACh release *CNS:* tremor, analgesia *Visceral smooth muscle:* contraction	*Visceral smooth muscle:* contraction *Iris:* constriction of pupil *Ciliary muscle:* contraction *Exocrine glands:* secretion *Vascular endothelium:* release of NO→ vasodilatation
2. Nature	Gq-protein coupled	Gi/Go-protein coupled	Gq-protein coupled
3. Transducer mechanism	IP_3/DAG—↑ cytosolic Ca^{2+}, PLA_2↑—PG synthesis	K^+ channel opening, ↓ cAMP	IP_3/DAG—↑ cytosolic Ca^{2+} PLA_2↑—PG synthesis
4. Agonists*	MCN-343A, Oxotremorine	Methacholine	Bethanechol
5. Antagonists*	Pirenzepine, Telenzepine	Methoctramine, Tripitramine	Solifenacin, Darifenacin

*Relatively selective
— ACh activates and atropine blocks all 3 subtypes of muscarinic receptors.
— The CNS contains all subtypes of muscarinic receptors, but M_1 appear to predominate.
— Most smooth muscles and glands have both M_2 and M_3 subtypes; M_3 predominates.

TABLE 7.4	Characteristics of subtypes of nicotinic receptor	
	N_M	N_N
1. Location and function subserved	*Neuromuscular junction:* depolarization of muscle end plate —contraction of skeletal muscle	*Autonomic ganglia:* depolarization —postganglionic impulse *Adrenal medulla:* catecholamine release *CNS:* site specific excitation or inhibition
2. Nature	Has intrinsic ion channel, pentamer of $\alpha 2\ \beta\ \epsilon$ or γ and δ subunits, each subunit has 4 TM segments	Has intrinsic ion channel, pentamer of only α or α,β subunits, each subunit has 4 TM segments
3. Transducer mechanism	Opening of cation (Na^+, K^+) channels	Opening of cation (Na^+, K^+, Ca^{2+}) channels
4. Agonists	PTMA, Nicotine	DMPP, Nicotine
5. Antagonists	Tubocurarine, α-Bungarotoxin	Hexamethonium, Trimethaphan

receptors as well which, like M_3 mediate contraction.

M₃: Visceral smooth muscle contraction and glandular secretions are elicited through M_3 receptors, which also mediate vasodilatation through EDRF release. Together the M_2 and M_3 receptors mediate most of the well-recognized muscarinic actions including contraction of LES.

The muscarinic receptors are G-protein coupled receptors having the characteristic 7 membrane traversing amino acid sequences. The M_1 and M_3 (also M_5) subtypes function through Gq protein and activate membrane bound phospholipase C (PLc)—generating inositol trisphosphate (IP_3) and diacylglycerol (DAG) which in turn release Ca^{2+} intracellularly—cause depolarization, glandular secretion, raise smooth muscle tone and release NO (from endothelium). They also activate phospholipase A_2 resulting in enhanced synthesis and release of prostaglandins and leucotrienes in certain tissues. The M_2 (and M_4) receptor opens K^+ channels (through $\beta\gamma$ subunits of regulatory protein Gi) and inhibits adenylyl cyclase (through α subunit of Gi) resulting in hyperpolarization, reduced pacemaker activity, slowing of conduction and decreased force of contraction in the heart. The M_4 receptor has been implicated in facilitation/inhibition of transmitter release in certain areas of the brain, while M_5 has been found to facilitate dopamine release and mediate reward behaviour.

Nicotinic These receptors are selectively activated by nicotine and blocked by tubocurarine or hexamethonium. They are rosette-like pentameric structures (*see* Fig. 4.4) which enclose a ligand gated cation channel: their activation causes opening of the channel and rapid flow of cations resulting in depolarization and an action potential. On the basis of location and selective agonists

and antagonists two subtypes N_M and N_N (previously labelled N_1 and N_2) are recognized (Table 7.4).

N$_M$: These are present at skeletal muscle endplate: are selectively stimulated by phenyl trimethyl ammonium (PTMA) and blocked by tubocurarine. They mediate skeletal muscle contraction.

N$_N$: These are present on ganglionic cells (sympathetic as well as parasympathetic), adrenal medullary cells (embryologically derived from the same site as ganglionic cells) and in spinal cord and certain areas of brain. They are selectively stimulated by dimethyl phenyl piperazinium (DMPP), blocked by hexamethonium, and constitute the primary pathway of transmission in ganglia.

CHOLINERGIC DRUGS
(Cholinomimetic, Parasympathomimetic)

These are drugs which produce actions similar to that of ACh, either by directly interacting with cholinergic receptors (cholinergic agonists) or by increasing availability of ACh at these sites *(anticholinesterases)*.

CHOLINERGIC AGONISTS

Choline esters	*Alkaloids*
Acetylcholine	Muscarine
Methacholine	Pilocarpine
Carbachol	Arecoline
Bethanechol	

ACTIONS (of ACh as prototype)

Depending on the type of receptor through which it is mediated, the peripheral actions of ACh are classified as muscarinic or nicotinic. The central actions are not so classifiable and are described separately.

A. Muscarinic actions

1. Heart ACh hyperpolarizes the SA nodal cells and decreases their rate of diastolic depolarization. As a result, rate of impulse generation is reduced—*bradycardia* or even cardiac arrest may occur.

At the A-V node and His-Purkinje fibres refractory period (RP) is increased and *conduction is slowed*: P-R interval increases and partial to complete A-V block may be produced. The *force of atrial contraction is markedly reduced* and RP of atrial fibres is abbreviated. Due to nonuniform vagal innervation, the intensity of effect on RP and conduction of different atrial fibres varies— inducing inhomogeneity and predisposing to atrial fibrillation or flutter.

Ventricular contractility is also decreased but the effect is not marked. The cardiac muscarinic receptors are of the M_2 subtype.

2. Blood vessels All blood vessels are dilated, though only few (skin of face, neck, salivary glands) receive cholinergic innervation. Fall in BP and flushing, especially in the blush area occurs. Muscarinic (M_3) receptors are present on vascular endothelial cells: vasodilatation is primarily mediated through the release of an *endothelium dependent relaxing factor* (EDRF) which is nitric oxide (NO). The PLc-IP$_3$/DAG pathway activates endothelial NO synthase through the Ca^+-Calmodulin mechanism. When the endothelium is damaged by disease, ACh can diffuse to the vascular smooth muscle and cause vasoconstriction *via* M_3 receptors located on their plasma membrane.

Stimulation of cholinergic nerves to the penis causes erection by releasing NO and dilating cavernosal vessels through M_3 receptors. However, this response is minimal with injected cholinomimetic drugs.

3. Smooth muscle Smooth muscle in most organs is contracted (mainly through M_3 receptors). Tone and peristalsis in the gastrointestinal tract is increased and sphincters relax →abdominal cramps and evacuation of bowel.

Peristalsis in ureter is increased. The detrusor muscle contracts while the bladder trigone and sphincter relaxes → voiding of bladder.

Bronchial muscles constrict, asthmatics are highly sensitive → bronchospasm, dyspnoea, precipitation of an attack of bronchial asthma.

4. Glands Secretion from all parasympathetically innervated glands is increased *via* M_3 and some M_2 receptors: sweating, salivation, lacrimation, increased tracheobronchial and gastric secretion. The effect on pancreatic and intestinal glands is not marked. Secretion of milk and bile is not affected.

5. Eye Contraction of circular muscle of iris → miosis.
Contraction of ciliary muscle → spasm of accommodation, increased outflow facility, reduction in intraocular tension (especially in glaucomatous patients).

B. Nicotinic actions

1. Autonomic ganglia Both sympathetic and parasympathetic ganglia are stimulated. This effect is manifested at higher doses. High dose of ACh given after atropine causes tachycardia and rise in BP due to stimulation of sympathetic ganglia and release of catecholamines.

2. Skeletal muscles Iontophoretic application of ACh to muscle endplate causes contraction of the fibre. Intraarterial injection of high dose can cause twitching and fasciculations, but i.v. injection is generally without any effect (due to rapid hydrolysis of ACh).

C. CNS actions

ACh injected i.v. does not penetrate blood-brain barrier and no central effects are seen. However, direct injection into the brain produces arousal response followed by depression. Cholinergic

TABLE 7.5	Properties of choline esters				
Choline ester	Hydrolysis by		Actions		Selective action on
	ACh E	BuChE	Musc.	Nico.	
Acetylcholine	++	+	+	+	Non selective
Methacholine	+	−	+	±	CVS
Carbachol	−	−	+	++	g.i.t., bladder
Bethanechol	−	−	+	−	g.i.t., bladder

drugs which enter brain produce complex behavioral and neurological effects.

The important features of other choline esters are summarized in Table 7.5.

Interactions Anticholinesterases potentiate ACh markedly, methacholine to less extent and have only additive action with carbachol or bethanechol, depending upon the role of ChE in the termination of action of the particular choline ester. Atropine and its congeners competitively antagonize muscarinic actions.

Adrenaline is a physiological antagonist.

Uses Choline esters are rarely, if ever, clinically used. ACh is not used because of evanescent and nonselective action. Methacholine was occasionally used to terminate paroxysmal supraventricular tachycardia but is obsolete now.

Bethanechol has been used in postoperative/postpartum nonobstructive urinary retention, neurogenic bladder to promote urination. It can afford symptomatic relief in congenital megacolon and gastroesophageal reflux, but is rarely used for these. Side effects are prominent: belching, colic, involuntary urination/defecation, flushing, sweating, fall in BP, bronchospasm.

Dose: 10–40 mg oral, 2.5–5 mg s.c.;
UROTONIN, BETHACOL 25 mg tab.

CHOLINOMIMETIC ALKALOIDS

Pilocarpine It is obtained from the leaves of *Pilocarpus microphyllus* and other species. It has prominent muscarinic actions and also stimulates ganglia—mainly through ganglionic muscarinic receptors.

Pilocarpine causes marked sweating, salivation and increase in other secretions. The cardiovascular effects are complex. Small doses generally cause fall in BP (muscarinic), but higher doses elicit rise in BP and tachycardia which is probably due to ganglionic stimulation (through ganglionic muscarinic receptors). Applied to the eye, it penetrates cornea and promptly causes miosis, ciliary muscle contraction and fall in intraocular tension lasting 4–8 hours.

Pilocarpine is used only in the eye as 0.5–4% drops. It is a third-line drug in open angle glaucoma. An initial stinging sensation in the eye and painful spasm of accommodation are frequent side effects. Other uses as a miotic are—to counteract mydriatics after they have been used for testing refraction and to prevent/break adhesions of iris with lens or cornea by alternating it with mydriatics.

Though it can be used as a sialogogue, no oral preparation is available.

PILOCAR 1%, 2%, 4% eye drops, CARPINE 0.5% eyedrops, PILODROPS 2% eyedrops.

Muscarine It occurs in poisonous mushrooms *Amanita muscaria* and *Inocybe* species and has only muscarinic actions. It is not used therapeutically but is of toxicological importance.

Mushroom poisoning Depending on the toxic principle present in the particular species, at least 3 types of mushroom poisoning is known.

Muscarine type (Early mushroom poisoning) due to *Inocybe* and related species. Symptoms characteristic of muscarinic actions appear within an hour of eating the mushroom, and are promptly reversed by atropine.

Hallucinogenic type It is due to muscimol and other isoxazole compounds which are present in *A. muscaria* and related mushrooms in much larger quantities than is muscarine. These compounds activate amino acid receptors, and block muscarinic receptors in the brain; have hallucinogenic property. Manifestations of poisoning are primarily central. There is no specific treatment and atropine is contraindicated. Another hallucinogenic mushroom is *Psilocybe mexicana* whose active principle psilocybine is a tryptaminergic (5-HT related) compound.

Phalloidin type (Late mushroom poisoning) It is due to peptide toxins found in *A. phalloides, Galerina* and related species. These inhibit RNA and protein synthesis. The symptoms start after many hours and are due to damage to the gastrointestinal mucosa, liver and kidney. Treatment consists of supportive measures. Thioctic acid may have some antidotal effect.

Arecoline It is found in betel nut *Areca catechu* and has muscarinic as well as nicotinic actions, including those on skeletal muscle endplate. It also has prominent CNS effect: has been tried in dementia as an enhancer of cognitive functions, but not found useful—has no therapeutic use.

ANTICHOLINESTERASES

Anticholinesterases (anti-ChEs) are agents which inhibit ChE, protect ACh from hydrolysis—produce cholinergic effects *in vivo* and potentiate ACh both *in vivo* and *in vitro*. Some anti ChEs have additional direct action on nicotinic cholinoceptors.

Reversible

Carbamates	*Acridine*
Physostigmine (Eserine)	Tacrine
Neostigmine	
Pyridostigmine	
Edrophonium	
Rivastigmine, Donepezil	
Galantamine	

Irreversible

Organophosphates	*Carbamates*
Dyflos (DFP)	Carbaryl* (SEVIN)
Echothiophate	Propoxur* (BAYGON)
Malathion*	
Diazinon* (TIK-20)	
Tabun£, Sarin£, Soman£	

*Insecticides
£Nerve gases for chemical warfare

CHEMISTRY

Anti-ChEs are either esters of carbamic acid or derivatives of phosphoric acid.
The generic formula of carbamates and organophosphates is shown below:

$$R_1-O-\overset{\overset{O}{\|}}{C}-N\underset{R_3}{\overset{R_2}{<}} \qquad \underset{R_3}{\overset{R_2}{>}}\overset{\overset{O}{\|}}{P}-R_1$$

CARBAMATES   ORGANOPHOSPHATES
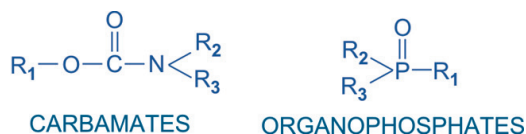
In carbamates R_1 may have a nonpolar tertiary amino N, e.g. in physostigmine, rendering the compound lipid soluble. In others, e.g. neostigmine, R_1 has a quaternary N^+—rendering it lipid insoluble. All organophosphates are highly lipid soluble except echothiophate which is water soluble.

MECHANISM OF ACTION

The anti-ChEs react with the enzyme essentially in the same way as ACh. The carbamates and phosphates respectively carbamylate and phosphorylate the esteratic site of the enzyme.

The mammalian AChE has been cloned and details of its structure as well as mode of interaction with ACh and various anti-ChEs has been worked out.

The active region of AChE forms a gorge which contains an *anionic site* (near glutamate 334) and an *esteratic site* formed by serine 203, and histidine 447 (Fig. 7.2A). Hydrolysis of ACh involves electrostatic attraction of positively charged N^+ of ACh to the anionic site (Fig. 7.2B) and nucleophilic attack by serine-OH which is activated by the adjacent histidine leading to acetylation of serine (Fig. 7.2C). The acetylated enzyme reacts with water to produce acetic acid and choline (Fig. 7.2D).

Whereas the acetylated enzyme reacts with water extremely rapidly and the esteratic site is freed in a fraction of a millisecond, the carbamylated enzyme (reversible inhibitors) reacts slowly (Fig. 7.2E, F) and the phosphorylated enzyme (irreversible inhibitors) reacts extremely slowly or not at all (Fig. 7.2G). It is noteworthy that edrophonium and tacrine attach only to the anionic site and do not form covalent bonds with the enzyme, while organophosphates attach only to the esteratic site forming covalent bonds. Reactivation of edrophonium-inhibited enzyme occurs in < 10 min, and does not involve hydrolysis of the inhibitor, but only its diffusion—action is brief. The half-life of reactivation of carbamylated enzyme (about 30 min) is less than that of synthesis of fresh enzyme protein, while that of phosphorylated enzyme (in days) is more than the regeneration time. The phosphorylated enzyme may also undergo 'aging' by the loss of one of the alkyl groups and become totally resistant to hydrolysis. Thus, apparently reversible and irreversible
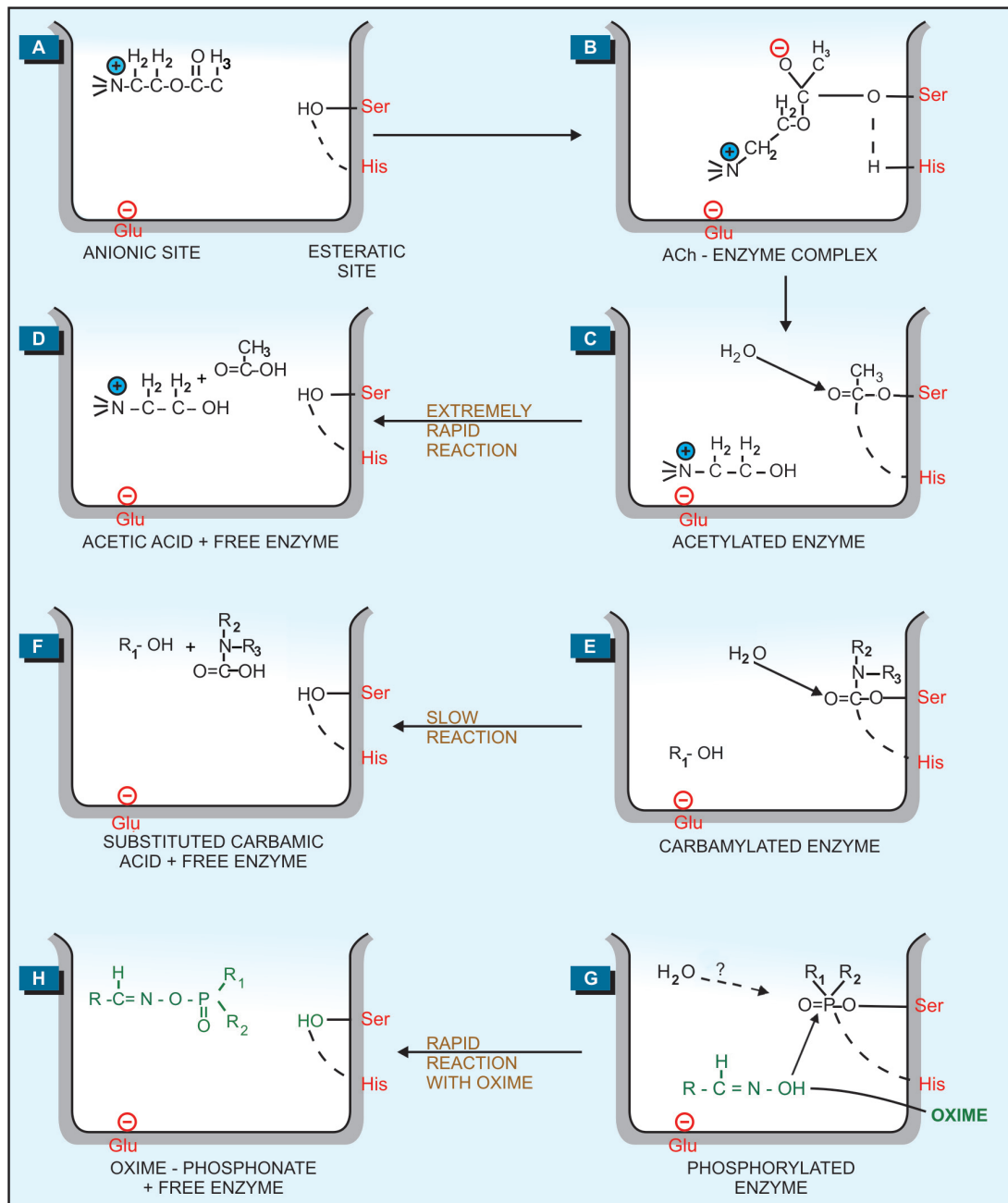
Fig. 7.2: Schematic representation of reaction of acetylcholine (A–D), or carbamate anticholinesterase (E, F), or organophosphate anticholinesterase (G) with cholinesterase enzyme; and reactivation of phosphorylated enzyme by oxime (G, H). Ser—Serine; His—Histidine; Glu—Glutamic acid.

enzyme inhibition is obtained, though the basic pattern of inhibitor-enzyme interaction remains the same.

PHARMACOLOGICAL ACTIONS

The actions of anti-ChEs are due to amplification of endogenous ACh. As such they are qualitatively similar to those of directly acting cholinoceptor stimulants. However, relative intensity of action on muscarinic, ganglionic, skeletal muscle and CNS sites varies among the different agents.

Lipid-soluble agents (physostigmine and organophosphates) have more marked muscarinic and CNS effects; stimulate ganglia but action on skeletal muscles is less prominent.

Lipid-insoluble agents (neostigmine and other quaternary ammonium compounds) produce more marked effect on the skeletal muscles (direct action on muscle endplate cholinoceptors as well), stimulate ganglia, but muscarinic effects are less prominent. They do not penetrate CNS and have no central effects.

Ganglia   Local hydrolysis of ACh is less important in ganglia: inactivation occurs partly by diffusion and hydrolysis in plasma. Anti-ChEs stimulate ganglia primarily through muscarinic receptors present there. High doses cause persistent depolarization of the ganglionic nicotinic receptors and blockade of transmission.

CVS   Cardiovascular effects are complex. Whereas muscarinic action would produce bradycardia and hypotension, ganglionic stimulation would tend to increase heart rate and BP. Action on medullary centres (stimulation followed by depression) further complicates the picture, so does ganglionic blockade with high doses. Thus, the overall effects are often unpredictable and depend on the agent and its dose.

Skeletal muscles   After treatment with anti-ChEs, the ACh released by a single nerve impulse is not immediately destroyed—rebinds to the same receptor, diffuses to act on neighbouring receptors and activates prejunctional fibres → repetitive firing → twitching and fasciculations. Force of

contraction in partially curarized and myasthenic muscles is increased. Higher doses cause persistent depolarization of endplates resulting in blockade of neuromuscular transmission → weakness and paralysis. Direct action of neostigmine and its congeners at the muscle endplates results in augmentation of these features.

CNS   Lipophilic anti-ChEs which penetrate into brain produce a generalized alerting response. Cognitive function may be improved in Alzheimer's disease. However, higher doses produce excitement, mental confusion, disorientation, tremors and convulsions followed by coma.

Other effects   These result from stimulation of smooth muscles and glands of the gastrointestinal, respiratory, urinary tracts and in the eye as described for ACh.

PHARMACOKINETICS

Physostigmine   It is rapidly absorbed from g.i.t. and parenteral sites. Applied to the eye, it penetrates cornea freely. It crosses blood-brain barrier and is disposed after hydrolysis by ChE.

Neostigmine and congeners   These are poorly absorbed orally; oral dose is 20–30 times higher than parenteral dose. They do not effectively penetrate cornea or cross blood-brain barrier. They are partially hydrolysed and partially excreted unchanged in urine.

Organophosphates   These are absorbed from all sites including intact skin and lungs. They are hydrolyzed as well as oxidized in the body and little is excreted unchanged.

INDIVIDUAL COMPOUNDS

The important features of physostigmine and neostigmine are presented in Table 7.6.

Physostigmine   eye drops are usually prepared freshly by ophthalmology departments.
BI-MIOTIC 0.25% eye drops with 2% pilocarpine nitrate.

Neostigmine   PROSTIGMIN, MYOSTIGMIN, TILSTIGMIN 15 mg tab, 0.5 mg/ml in 1 ml and 5 ml inj.

TABLE 7.6	Comparative features of physostigmine and neostigmine	
	Physostigmine	*Neostigmine*
1. Source	Natural alkaloid from *Physostigma venenosum* (Calabar bean)	Synthetic
2. Chemistry	Tertiary amine derivative	Quaternary ammonium compound
3. Oral absorption	Good	Poor
4. CNS actions	Present	Absent
5. Applied to eye	Penetrates cornea	Poor penetration
6. Direct action on N_M cholinoceptors	Absent	Present
7. Prominent effect on	Autonomic effectors	Skeletal muscles
8. Important use	Miotic (glaucoma)	Myasthenia gravis
9. Dose	0.5–1 mg oral/parenteral 0.1–1.0% eye drops	0.5–2.5 mg i.m./s.c. 15–30 mg orally
10. Duration of action	Systemic 4–6 hrs In eye 6 to 24 hrs	3–4 hrs.

Pyridostigmine   Resembles neostigmine in all respects but is dose to dose less potent and longer acting, less frequent dosing is required in myasthenia gravis.

DISTINON, MYESTIN 60 mg tab; 1–3 tab TDS.

Ambenonium is another longacting congener used in myasthenia.

Edrophonium   Resembles neostigmine in action, has a brief duration (10–30 min), suitable only as a diagnostic agent for myasthenia gravis.
Dose: 2–10 mg i.v.

Tacrine   It is a lipophilic acridine compound which interacts with ChE in a manner analogous to edrophonium. It crosses blood-brain barrier and has a longer duration of action. By increasing brain ACh levels it was found to produce some symptomatic improvement in Alzheimer's disease, but has gone into disuse due to hepatotoxicity (*see* Ch. 35).

Rivastigmine   This lipophilic relatively cerebroselective ChE inhibitor has been introduced for Alzheimer's disease (AD), *see* Ch. 35.

Donepezil   Another centrally acting anti-AChE that has produced cognitive and behavioral improvement in AD. It is long-acting and suitable for once daily administration (*see* Ch. 35).

Galantamine   This natural alkaloid inhibitor of cerebral AChE has in addition weak agonistic action on nicotinic receptors. It is being used to afford symptomatic relief in AD (*see* Ch. 35).

Dyflos   It is Diisopropyl-fluoro-phosphate (DFP), a very potent and long-acting anti-ChE. It is now obsolete as a miotic.

Echothiophate   It is an organophosphate with quaternary structure. It is water soluble; and was used as a long acting miotic.

Precautions   Anti-ChEs are contraindicated in sick sinus, A-V conduction defects and hypotensive states. They are to be used cautiously in peptic ulcer, asthma, COPD and seizure patients.

USES

1. As miotic

(a) In glaucoma: Miotics increase the tone of ciliary muscle (attached to scleral spur) and sphincter pupillae which pull on and somehow improve alignment of the trabeculae so that outflow facility is increased → i.o.t. falls in open angle glaucoma.

Pilocarpine is the preferred miotic. The action is rapid and short lasting (4–6 hr); 6–8 hourly instillation is required and even then i.o.t. may fluctuate inbetween. Diminution of vision, especially in dim light (due to constricted pupil), spasm of accommodation and brow pain are frequent side effects. Systemic effects—nausea, diarrhoea, sweating and bronchospasm may occur with higher concentration eye drops.

Physostigmine (0.1%) is used only to supplement pilocarpine. Miotics are now 3rd choice drugs, used only as add on therapy in advanced cases. However, they are effective in aphakic glaucoma. Pilocarpine (along with other drugs) is used in angle closure glaucoma as well.

(b) To reverse the effect of mydriatics after refraction testing.

(c) To prevent formation of adhesions between iris and lens or iris and cornea, and even to break those which have formed due to iritis, corneal ulcer, etc.—a miotic is alternated with a mydriatic.

2. Myasthenia gravis

Myasthenia gravis is an autoimmune disorder affecting about 1 in 10,000 population, due to development of antibodies directed to the nicotinic receptors (NR) at the muscle endplate → reduction in number of free N_M cholinoceptors to 1/3 of normal or less (Fig. 7.3) and structural damage to the neuromuscular junction. This results in weakness and easy fatigability on repeated activity, with recovery after rest. The eyelid, external ocular, facial and pharyngeal muscles are generally involved first. Later, limb and respiratory muscles get affected. Neostigmine and its congeners improve muscle contraction by allowing ACh released from prejunctional endings to accumulate and act on the receptors over a larger area, as well as by directly depolarizing the endplate.
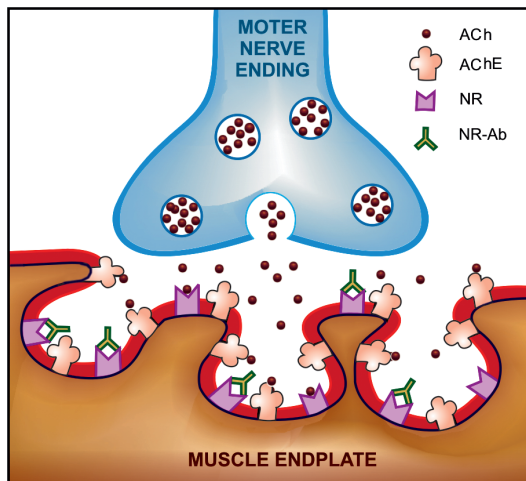

Fig. 7.3: Neuromuscular junction of myasthenic muscle In myasthenia gravis the population of nicotinic receptors (NR) available at muscle endplate for binding acetylcholine (ACh) is markedly reduced due to their obliteration by nicotinic receptor antibodies (NR-Ab). Acetylcholinesterase (AChE) molecules located strategically at the muscle endplate rapidly hydrolyse ACh. Anticholinesterases inhibit AChE, allowing the same ACh molecules to repeatedly interact with the available NRs; frequency of ACh-NR interaction is increased

Treatment is usually started with *neostigmine* 15 mg orally 6 hourly; dose and frequency is then adjusted to obtain optimum relief from weakness. However, the dosage requirement may fluctuate from time to time and there are often unpredictable periods of remission and exacerbation. Pyridostigmine is an alternative which needs less frequent dosing. If intolerable muscarinic side effects are produced, atropine can be added to block them. These drugs have no effect on the basic disorder which often progresses; ultimately it may not be possible to restore muscle strength adequately with anti-ChEs alone.

Corticosteroids afford considerable improvement in such cases by their immunosuppressant action. They inhibit production of NR-antibodies and may increase synthesis of NRs. However, their long term use has problems of its own (*see* Ch. 20). Prednisolone 30–60 mg/day induces remission in about 80% of the advanced cases; 10 mg daily or on alternate days can be used for maintenance therapy. Other immunosuppressants have also been used with benefit in advanced cases. Both azathioprine and cyclosporine also inhibit NR-antibody synthesis by affecting T-cells, but response to the former is slow in onset (takes upto 1 year), while that to the latter is relatively quick (in 1–2 months).

Removal of antibodies by *plasmapheresis* (plasma exchange) is another therapeutic approach. Dramatic but short lived improvement can often be achieved by it in myasthenic crisis.

Thymectomy is effective in a majority of the cases. It produces gradual improvement and even complete remission has been obtained. Thymus may contain modified muscle cells with NRs on their surface, which may be the source of the antigen for production of anti-NR antibodies in myasthenic patients.

Myasthenic crisis is characterized by acute weakness of respiratory muscles. It is managed by tracheal intubation and mechanical ventilation. Generally, i.v. methylprednisolone pulse therapy is given while anti-ChEs are withheld for 2–3 days followed by their gradual reintroduction.

CHAPTER 7

Most patients can be weaned off the ventilator in 1–3 weeks. Plasmapheresis hastens recovery.

Overtreatment with anti-ChEs   If the dose of the antiChE is not adjusted according to the fluctuating requirement, relative overdose may occur from time-to-time. Overdose also produces weakness by causing persistent depolarization of muscle endplate, and is called *cholinergic weakness*. Late cases with high anti-ChE dose requirements often alternately experience myasthenic and cholinergic weakness and these may assume crisis proportions.

The two types of weakness require opposite treatments. They can be differentiated by *edrophonium test*—

Inject edrophonium (2 mg. i.v.) → improvement→myasthenic crisis

no improvement or worsening→cholinergic crisis
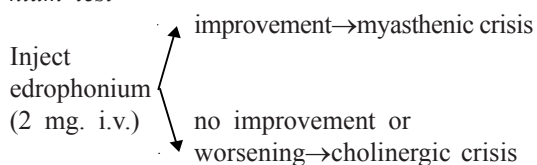
Diagnostic tests for myasthenia gravis
(a) *Ameliorative test:* Initially edrophonium 2 mg is injected i.v. as a test dose. If nothing untoward happens, the remaining 8 mg is injected after 30–60 sec. Reversal of weakness and short-lasting improvement in the strength of affected muscles occurs only in myasthenia gravis and not in other muscular dystrophies.

In case edrophonium is not available, the test can be performed with 1.5 mg i.v. neostigmine. Atropine pretreatment may be given to block the muscarinic effects of neostigmine.
(b) *Provocative test:* myasthenics are highly sensitive to d-tubocurarine; 0.5 mg i.v. causes marked weakness in them but is ineffective in non-myasthenics. This test is hazardous: facilities for positive pressure respiration must be at hand before performing it. This test is better not performed.
(c) Demonstration of anti-NR antibodies in plasma or muscle biopsy specimen is a more reliable test.

3. Postoperative paralytic ileus/urinary retention   This may be relieved by 0.5–1 mg s.c. neostigmine, provided no organic obstruction is present.

4. Postoperative decurarization Neostigmine 0.5–2.0 mg (30–50 μg/kg) i.v., preceded by atropine or glycopyrrolate 10 μg/kg to block muscarinic effects, rapidly reverses muscle paralysis induced by competitive neuromuscular blockers.

5. Cobra bite   Cobra venom has a curare like neurotoxin. Though specific antivenom serum is the primary treatment, neostigmine + atropine prevent respiratory paralysis.

6. Belladonna poisoning   Physostigmine 0.5–2 mg i.v. repeated as required is the specific antidote for poisoning with belladonna or other anticholinergics. It penetrates blood-brain barrier and antagonizes both central and peripheral actions. However, physostigmine often itself induces hypotension, arrhythmias and undesirable central effects. It is therefore employed only as a last resort. Neostigmine does not block the central effect, but is less risky.

7. Other drug overdosages   Tricyclic antidepressants, phenothiazines and many antihistaminics have additional anticholinergic property. Overdose symptoms and coma produced by these drugs are partly antagonized by physostigmine. However, it may worsen the fall in BP and arrhythmias; use therefore is risky. Physostigmine also appears to have a modest nonspecific arousal effect in CNS depression produced by diazepam or general anaesthetics, but use for this purpose is rarely warranted.

8. Alzheimer's disease   Characterized by progressive dementia, AD is a neurodegenerative disorder, primarily affecting cholinergic neurones in the brain. Various measures to augment cholinergic transmission in the brain have been tried. The relatively cerebroselective anti-ChEs, *rivastigmine, donepezil* and *galantamine* are now commonly used. For details *see* Ch. 35.

ANTICHOLINESTERASE POISONING

Anticholinesterases are easily available and extensively used as agricultural and household insecticides; accidental as well as suicidal and homicidal poisoning is common.

Local muscarinic manifestations at the site of exposure (skin, eye, g.i.t.) occur immediately and are followed by complex systemic effects due to muscarinic, nicotinic and central actions. They are—
• Irritation of eye, lacrimation, salivation, sweating, copious tracheo-bronchial secretions, miosis, blurring of vision, bronchospasm, breathlessness, colic, involuntary defecation and urination.

- Fall in BP, bradycardia or tachycardia, cardiac arrhythmias, vascular collapse.
- Muscular fasciculations, weakness, respiratory paralysis (central as well as peripheral).
- Irritability, disorientation, unsteadiness, tremor, ataxia, convulsions, coma and death.
- Death is generally due to respiratory failure.

Treatment

1. Termination of further exposure to the poison— fresh air, wash the skin and mucous membranes with soap and water, gastric lavage according to need.
2. Maintain patent airway, positive pressure respiration if it is failing.
3. Supportive measures—maintain BP, hydration, control of convulsions with judicious use of diazepam.
4. Specific antidotes—

(a) *Atropine* It is highly effective in counter-acting the muscarinic symptoms, but higher doses are required to antagonize the central effects. It does not reverse peripheral muscular paralysis which is a nicotinic action. All cases of anti-ChE (carbamate or organophosphate) poisoning must be promptly given atropine 2 mg i.v. repeated every 10 min till dryness of mouth or other signs of atropinization appear (upto 200 mg has been administered in a day). Continued treatment with maintenance doses may be required for 1–2 weeks.

(b) *Cholinesterase reactivators* Oximes are used to restore neuromuscular transmission only in case of organophosphate anti-ChE poisoning. The phosphorylated ChE reacts very slowly or not at all with water. However, if more reactive OH groups in the form of oximes (generic formula R–CH = N–OH) are provided, reactivation occurs more than a million times faster (*see* Fig. 7.2G and H).

Pralidoxime (2-PAM) has a positively charged quaternary nitrogen: attaches to the anionic site of the enzyme which remains unoccupied in the presence of organophosphate inhibitors. Its oxime end reacts with the phosphorus atom attached to the esteratic site: the oxime-phosphonate so formed diffuses away leaving the reactivated ChE. Pralidoxime is ineffective as an antidote to carbamate anti-ChEs (physostigmine, neostigmine, carbaryl, propoxur) in which case the anionic site of the enzyme is not free to provide attachment to it. It is rather contraindicated in carbamate poisoning, because not only it does not reactivate carbamylated enzyme, it has weak anti-ChE activity of its own.

Pralidoxime (NEOPAM, PAM-A INJ. 500 mg/20 ml infusion, LYPHE 1 g/vial for inj.) is injected i.v. slowly in a dose of 1–2 g (children 20–40 mg/kg). Another regimen is 30 mg/kg i.v. loading dose, followed by 8–10 mg/kg/hour continuous infusion till recovery. Pralidoxime causes more marked reactivation of skeletal muscle ChE than at autonomic sites and not at all in the CNS (does not penetrate into brain). Treatment should be started as early as possible (within few hours), before the phosphorylated enzyme has undergone 'aging' and become resistant to hydrolysis. Doses may be repeated according to need (max. 12 g in first 24 hrs. Lower doses according to symptoms are continued 1–2 weeks). The use of oximes in organophosphate poisoning is secondary to that of atropine. Moreover, the clinical benefit of oxime therapy is highly variable depending upon the compound involved (different organophosphates 'age' at different rates), the amount of poison that has entered the body, time lapse before therapy is started and dose of the oxime.

Other oximes are obidoxime (more potent than pralidoxime) and diacetyl-monoxime (DAM), which is lipophilic.

Chronic organophosphate poisoning Repeated exposure to certain fluorine containing and triaryl organophosphates results in polyneuritis and demyelination after a latent period of days to weeks. Sensory disturbances occur first followed by muscle weakness, tenderness and depressed tendon reflexes—lower motor neurone paralysis. In the second phase, spasticity and upper motor neurone paralysis gradually supervenes. Recovery may take years. The mechanism of this toxicity is not known, but it is not due to inhibition of ChE; there is no specific treatment.

☞ PROBLEM DIRECTED STUDY

7.1 A man aged 45 years presented with gradual onset complaints of double vision, drooping eyelids, difficulty in chewing food and weakness of limbs which is accentuated by exercise. The symptoms fluctuate in intensity over time. A provisional diagnosis of myasthenia gravis is made.

(a) Can a pharmacological test be performed to confirm/refute the diagnosis?

(b) In case the diagnosis is confirmed, can this disease be cured by medication?

(c) Is there a surgical solution for this illness?

(see Appendix-1 for solution)

ANTICHOLINERGIC DRUGS (Muscarinic receptor antagonists, Atropinic, Parasympatholytic)

Conventionally, the term 'anticholinergic drugs' is restricted to those which block actions of ACh on autonomic effectors and in the CNS exerted through muscarinic receptors. Though nicotinic receptor antagonists also block certain actions of ACh, they are generally referred to as 'ganglion blockers' and 'neuromuscular blockers'.

Atropine, the prototype drug of this class, is highly selective for muscarinic receptors, but some of its synthetic substitutes do possess significant nicotinic blocking property in addition. The selective action of atropine can easily be demonstrated on a piece of guinea pig ileum where ACh induced contractions are blocked without affecting those evoked by histamine, 5-HT or other spasmogens. The selectivity is, however, lost at very high doses. All anticholinergics are competitive antagonists.

CLASSIFICATION

1. *Natural alkaloids* Atropine, Hyoscine (Scopolamine).
2. *Semisynthetic derivatives* Homatropine, Atropine methonitrate, Hyoscine butyl bromide, Ipratropium bromide, Tiotropium bromide.
3. *Synthetic compounds*
(a) *Mydriatics:* Cyclopentolate, Tropicamide.
(b) *Antisecretory-antispasmodics*:
   (i) *Quaternary compounds:* Propantheline, Oxyphenonium, Clidinium, Pipenzolate methyl bromide, Isopropamide, Glycopyrrolate.
   (ii) *Tertiary amines:* Dicyclomine, Valethamate, Pirenzepine.
(c) *Vasicoselective:* Oxybutynin, Flavoxate, Tolterodine.
(d) *Antiparkinsonian:* Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.

In addition, many other classes of drugs, i.e. tricyclic antidepressants, phenothiazines, antihistamines and disopyramide possess significant antimuscarinic actions.

The natural alkaloids are found in plants of the solanaceae family. The levo-isomers are much more active than the dextroisomers. Atropine is racemic while scopolamine is *l*-hyoscine.

PHARMACOLOGICAL ACTIONS
(Atropine as prototype)

The actions of atropine can be largely predicted from knowledge of parasympathetic responses. Prominent effects are seen in organs which normally receive strong parasympathetic tone. Atropine blocks all subtypes of muscarinic receptors.

1. CNS Atropine has an overall CNS stimulant action. However, these effects are not appreciable at low doses which produce only peripheral effects because of restricted entry into the brain. Hyoscine produces central effects (depressant) even at low doses.
- Atropine stimulates many medullary centres —vagal, respiratory, vasomotor.
- It depresses vestibular excitation and has antimotion sickness property. The site of this action is not clear—probably there is a cholinergic link in the vestibular pathway, or it may be exerted at the cortical level.
- By blocking the relative cholinergic overactivity in basal ganglia, it suppresses tremor and rigidity of parkinsonism.

- High doses cause cortical excitation, restlessness, disorientation, hallucinations and delirium followed by respiratory depression and coma.

Majority of the central actions are due to blockade of muscarinic receptors in the brain, but some actions may have a different basis.

2. CVS

Heart The most prominent effect of atropine is tachycardia. It is due to blockade of M_2 receptors on the SA node through which vagal tone decreases HR. Higher the existing vagal tone— more marked is the tachycardia (maximum in young adults, less in children and elderly). On i.m./s.c. injection transient initial bradycardia often occurs. Earlier believed to be due to stimulation of vagal centre, it is now thought to be caused by blockade of muscarinic autoreceptors (M_1) on vagal nerve endings, thereby augmenting ACh release. This is suggested by the finding that selective M_1 antagonist pirenzepine is equipotent to atropine in causing bradycardia. Moreover, atropine substitutes which do not cross blood-brain barrier also produce initial bradycardia. Atropine abbreviates refractory period of A-V node and facilitates A-V conduction, especially if it has been depressed by high vagal tone. P-R interval is shortened.

BP Since cholinergic impulses are not involved in the maintenance of vascular tone, atropine does not have any consistent or marked effect on BP. Tachycardia and vasomotor centre stimulation tend to raise BP, while histamine release and direct vasodilator action (at high doses) tend to lower BP.

Atropine blocks vasodepressor action of cholinergic agonists.

3. Eye
The autonomic control of iris muscles and the action of mydriatics as well as miotics is illustrated in Fig. 8.1. Topical instillation of atropine causes mydriasis, abolition of light reflex and cycloplegia lasting 7–10 days. This results in photophobia and blurring of near vision. The ciliary muscles recover somewhat earlier than sphincter pupillae. The intraocular tension tends to rise, especially in narrow angle glaucoma.
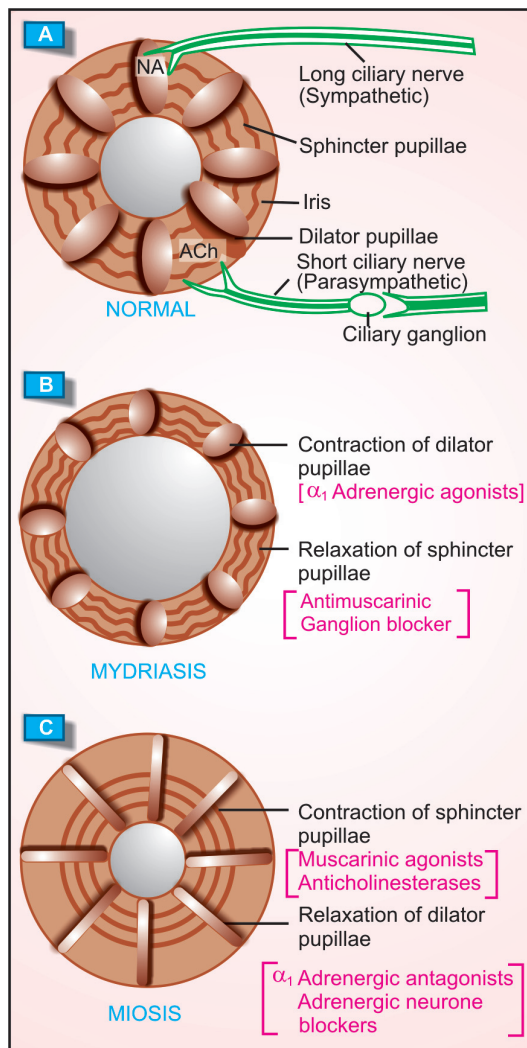
Fig. 8.1: Autonomic control of pupil (A); and site of action of mydriatics (B) and miotics (C)

However, conventional systemic doses of atropine produce minor ocular effects.

4. Smooth muscles
All visceral smooth muscles that receive parasympathetic motor innervation are relaxed by atropine (M_3 blockade). Tone and amplitude of contractions of stomach and intestine are reduced; the passage of chyme is slowed—constipation may occur, spasm may be relieved. However, peristalsis is only incompletely suppressed because it is

primarily regulated by local reflexes in the enteric plexus, and other neurotransmitters (5-HT, enkephalin, etc.) are involved. Enhanced motility due to injected cholinergic drugs is more completely antagonised than that due to vagal stimulation, because intramural neurones which are activated by vagus utilize a number of noncholinergic transmitters as well.

Atropine causes bronchodilatation and reduces airway resistance, especially in COPD and asthma patients. Inflammatory mediators like histamine, PGs, leucotrienes and kinins which participate in asthma increase vagal activity in addition to their direct stimulant action on bronchial muscle and glands. Atropine attenuates their action by antagonizing the reflex vagal component.

Atropine has relaxant action on ureter and urinary bladder; urinary retention can occur in older males with prostatic hypertrophy. However, this relaxant action can be beneficial for increasing bladder capacity and controlling detrusor hyperreflexia in neurogenic bladder/enuresis. Relaxation of biliary tract is less marked and effect on uterus is minimal.

5. Glands Atropine markedly decreases sweat, salivary, tracheobronchial and lacrimal secretion (M_3 blockade). Skin and eyes become dry, talking and swallowing may be difficult.

Atropine decreases secretion of acid, pepsin and mucus in the stomach, but the primary action is on volume of secretion so that pH of gastric contents may not be elevated unless diluted by food. Since bicarbonate secretion is also reduced, rise in pH of fasting gastric juice is only modest. Relatively higher doses are needed and atropine is less efficacious than H_2 blockers in reducing acid secretion. Intestinal and pancreatic secretions are not significantly reduced. Bile production is not under cholinergic control, so not affected.

6. Body temperature Rise in body temperature occurs at higher doses. It is due to both inhibition of sweating as well as stimulation of temperature regulating centre in the hypothalamus. Children are highly susceptible to atropine fever.

7. Local anaesthetic Atropine has a mild anaesthetic action on the cornea.

Atropine has been found to enhance ACh (also NA) release from certain postganglionic parasympathetic and sympathetic nerve endings, and thus produce paradoxical responses. This is due to blockade of release inhibitory muscarinic autoreceptors present on these nerve terminals.

The sensitivity of different organs and tissues to atropine varies and can be graded as—

Saliva, sweat, bronchial secretion > eye, bronchial muscle, heart > smooth muscle of intestine, bladder > gastric glands and smooth muscle.

The above differences probably reflect the relative dependence of the function on cholinergic tone *vis a vis* other influences, and variation in synaptic gaps in different organs. The pattern of relative activity is nearly the same for other atropine substitutes except *pirenzepine* which inhibits gastric secretion at doses that have little effect on other secretions, heart and eye. This is probably because atropine equally blocks M_1, M_2 and M_3 receptors whereas pirenzepine is a selective M_1 antagonist.

Atropine more effectively blocks responses to exogenously administered cholinergic drugs than those to parasympathetic nerve activity. This may be due to release of ACh very close to the receptors by nerves and involvement of cotransmitters (*see* p. 97).

Hyoscine This natural anticholinergic alkaloid differs from atropine in many respects, these are tabulated in Table 8.1.

PHARMACOKINETICS

Atropine and hyoscine are rapidly absorbed from g.i.t. Applied to eyes they freely penetrate cornea. Passage across blood-brain barrier is somewhat restricted. About 50% of atropine is metabolized in liver and rest is excreted unchanged in urine. It has a $t\frac{1}{2}$ of 3–4 hours. Hyoscine is more completely metabolized and has better blood-brain barrier penetration.

Atropine sulfate: 0.6–2 mg i.m., i.v. (children 10 µg/kg), 1–2% topically in eye. ATROPINE SULPHATE: 0.6 mg/ml inj., 1% eye drop/ointment; ATROSULPH 1% eye drop, 5% eye oint. Hyoscine hydrobromide: 0.3–0.5 mg oral, i.m.; also as transdermal patch.
Combinations of atropine with analgesics and antipyretics are banned in India.

TABLE 8.1	Comparative features of atropine and hyoscine	
	Atropine	Hyoscine
1. Chief source	Atropa belladonna, Datura stramonium	Hyoscyamys niger
2. Alkaloidal ester of tropic acid with	Tropine (base)	Scopine (base)
3. CNS effect low dose high dose	Excitatory Excitation (mild) Excitation (strong)	Depressant (amnesia, fatigue, drowsiness, N-REM sleep) Excitation
4. Anticholinergic property	More potent on heart, bronchial muscle and intestines	More potent on eye and secretory glands
5. Duration of action	Longer	Shorter
6. Anti-motion sickness	+ +	+ + +

ATROPINE SUBSTITUTES

Many semisynthetic derivatives of belladonna alkaloids and a large number of synthetic compounds have been introduced with the aim of producing more selective action on certain functions. Most of these differ only marginally from the natural alkaloids, but some recent ones appear promising.

Quaternary compounds

These have certain common features—
• Incomplete oral absorption.
• Poor penetration in brain and eye; central and ocular effects are not seen after parenteral/oral administration.
• Elimination is generally slower; majority are longer acting than atropine.
• Have higher nicotinic blocking property. Some ganglionic blockade may occur at clinical doses → postural hypotension, impotence are additional side effects.
• At high doses some degree of neuromuscular blockade may also occur.

Drugs in this category are—

1. *Hyoscine butyl bromide* 20–40 mg oral, i.m., s.c., i.v.; less potent and longer acting than atropine; used for esophageal and gastrointestinal spastic conditions.
BUSCOPAN 10 mg tab., 20 mg/ml amp.

2. *Atropine methonitrate* 2.5–10 mg oral, i.m.; for abdominal colics and hyperacidity.
MYDRINDON 1 mg (adult), 0.1 mg (child) tab; in SPASMOLYSIN 0.32 mg tab;

3. *Ipratropium bromide* 40–80 µg by inhalation; it acts selectively on bronchial muscle without altering volume or consistency of respiratory secretions. Another desirable feature is that in contrast to atropine, it does not depress muco-ciliary clearance by bronchial epithelium. It has a gradual onset and late peak (at 40–60 min) of bronchodilator effect in comparison to inhaled sympathomimetics. Thus, it is more suitable for regular prophylactic use rather than for rapid symptomatic relief during an attack. Action lasts 4–6 hours. It acts on receptors located mainly in the larger central airways (contrast sympathomimetics whose primary site of action is peripheral bronchioles, *see* Fig. 16.2). The parasympathetic tone is the major reversible factor in chronic obstructive pulmonary disease (COPD). Therefore, ipratropium is more effective in COPD than in bronchial asthma. Transient local side effects like dryness of mouth, scratching sensation in trachea, cough, bad taste and nervousness are reported in 20–30% patients, but systemic effects are rare because of poor absorption from the lungs and g.i.t. (major fraction of any inhaled drug is swallowed).
IPRAVENT 20 µg and 40 µg/puff metered dose inhaler, 2 puffs 3–4 times daily; 250 µg/ml respirator soln., 0.4–2 ml nebulized in conjunction with a β_2 agonist 2–4 times daily.

Also used to control rhinorrhoea in perennial rhinitis and common cold; IPRANASE-AQ 0.084% nasal spray (42 µg per actuation), 1–2 sprays in each nostril 3–4 times a day.

4. *Tiotropium bromide*   A newer congener of ipratropium bromide which binds very tightly to bronchial M_1/M_3 muscarinic receptors producing long lasting bronchodilatation. Binding to M_2 receptors is less tight confering relative M_1/M_3 selectivity (less likely to enhance ACh release from vagal nerve endings in lungs due to M_2 receptor blockade). Like ipratropium, it is not absorbed from respiratory and g.i. mucosa and has exhibited high bronchial selectivity of action.
TIOVA 18 µg rotacaps; 1 rotacap by inhalation OD.

5. *Propantheline*   15–30 mg oral; it was a popular anticholinergic drug used for peptic ulcer and gastritis. It has some ganglion blocking activity as well and is claimed to reduce gastric secretion at doses which produce only mild side effects. Gastric emptying is delayed and action lasts for 6–8 hours. Use has declined due to availability of H_2 blockers and proton pump inhibitors.
PROBANTHINE 15 mg tab.

6. *Oxyphenonium*   5–10 mg (children 3–5 mg) oral; similar to propantheline, recommended for peptic ulcer and gastrointestinal hypermotility.
ANTRENYL 5, 10 mg tab.

7. *Clidinium*   2.5–5 mg oral; This antisecretory-antispasmodic has been used in combination with benzodiazepines for nervous dyspepsia, gastritis, irritable bowel syndrome, colic, peptic ulcer, etc.
In SPASRIL, ARWIN 2.5 mg tab with chlordiazepoxide 5 mg. NORMAXIN, CIBIS 2.5 mg with dicyclomine 10 mg and chlordiazepoxide 5 mg.

8. *Pipenzolate methyl bromide*   5–10 mg (children 2–3 mg) oral; It has been promoted especially for flatulent dyspepsia, infantile colics and abdominal cramps.
In PIPEN 4 mg + dimethylpolysiloxane 40 mg/ml drops.

9. *Isopropamide*   5 mg oral; indicated in hyperacidity, nervous dyspepsia, irritable bowel and other gastrointestinal problems, specially when associated with emotional/mental disorders.
In STELABID, GASTABID 5 mg tab. with trifluoperazine 1 mg.

10. *Glycopyrrolate*   0.1–0.3 mg i.m. (5–10 µg/kg), potent and rapidly acting antimuscarinic lacking central effects. Almost exclusively used for preanaesthetic medication and during anaesthesia. GLYCO-P 0.2 mg/ml amp., 1 mg in 5 ml vial, PYROLATE 0.2 mg/ml, 1 ml amp, 10 ml vial.

Tertiary amines

1. *Dicyclomine*   20 mg oral/i.m., children 5–10 mg; has direct smooth muscle relaxant action in addition to weak anticholinergic. It exerts antispasmodic action at doses which produce few atropinic side effects. However, infants have exhibited atropinic toxicity symptoms and it is not recommended below 6 months of age. It also has antiemetic property: has been used in morning sickness and motion sickness. Dysmenorrhoea and irritable bowel are other indications.
CYCLOSPAS-D, 20 mg with dimethicone 40 mg tab; CYCLOPAM INJ. 10 mg/ml in 2 ml, 10 ml, 30 ml amp/vial, also 20 mg tab with paracetamol 500 mg; in COLIMEX, COLIRID 20 mg with paracetamol 500 mg tab, 10 mg/ml drops with dimethicone.

2. *Valethamate:* The primary indication of this anticholinergic-smooth muscle relaxant is to hasten dilatation of cervix when the same is delayed during labour, and as visceral antispasmodic, urinary, biliary, intestinal colic.
Dose: 8 mg i.m., 10 mg oral repeated as required.
VALAMATE 8 mg in 1 ml inj, EPIDOSIN 8 mg inj., 10 mg tab.

3. *Pirenzepine*   100–150 mg/day oral; it selectively blocks M_1 muscarinic receptors (*see* p. 101) and inhibits gastric secretion without producing typical atropinic side effects (these are due to blockade of M_2 and M_3 receptors). The more likely site of action of pirenzepine in stomach is intramural plexuses and ganglionic cells rather than the parietal cells themselves. It is nearly equally effective as cimetidine in relieving peptic ulcer pain and promoting ulcer healing, but has been overshadowed by H_2 blockers and proton pump inhibitors.

Vasicoselective drugs

1. *Oxybutynin*   This newer antimuscarinic has high affinity for receptors in urinary bladder and salivary glands alongwith additional smooth muscle relaxant and local anaesthetic properties. It is relatively selective for M_1/M_3 subtypes with less action on the M_2 subtype. Because of vasicoselective action, it is used for detrusor instability resulting in urinary frequency and urge

incontinence. Beneficial effects have been demonstrated in post-prostatectomy vasical spasm, neurogenic bladder, spina bifida and nocturnal enuresis. Anticholinergic side effects are common after oral dosing, but intravasical instillation increases bladder capacity with few side effects. Oxybutynin is metabolized by CYP3A4; its dose should be reduced in patients being treated with inhibitors of this isoenzyme.

Dose: 5 mg BD/TDS oral; children above 5 yr 2.5 mg BD.
OXYBUTIN, CYSTRAN, OXYSPAS 2.5 mg and 5 mg tabs.

2. *Tolterodine:* This relatively M_3 selective muscarinic antagonist has preferential action on urinary bladder; less likely to cause dryness of mouth and other anticholinergic side effects. It is indicated in overactive bladder with urinary frequency and urgency. Since it is metabolized by CYP3A4, dose should be halved in patients receiving CYP3A4 inhibitors (erythromycin, ketoconazole, etc.)

Dose: 1–2 mg BD or 2–4 mg OD of sustained release tab. oral.
ROLITEN, TOLTER 1, 2 mg tabs, TORQ 2, 4 mg SR tab.

3. *Flavoxate* has properties similar to oxybutynin and is indicated in urinary frequency, urgency and dysuria associated with lower urinary tract infection.

URISPAS, FLAVATE, FLAVOSPAS 200 mg tab, 1 tab TDS.

Darifenacin and *Solifenacin* are other relatively M_3 subtype selective antimuscarinics useful in bladder disorders.

Drotaverine It is a novel non-anticholinergic smooth muscle antispasmodic which acts by inhibiting phosphodiesterase-4 (PDE-4) selective for smooth muscle. Elevation of intracellular cAMP/cGMP attends smooth muscle relaxation. Changes in membrane ionic fluxes and membrane potential have also been shown. It has been used orally as well as parenterally in intestinal, biliary and renal colics, irritable bowel syndrome, uterine spasms, etc. without anticholinergic side effects. Adverse effects reported are headache, dizziness, constipation and flushing. Fall in BP can occur on i.v. injection.

Dose: 40–80 mg TDS; DROTIN, DOTARIN, DOVERIN 40, 80 mg tabs, 40 mg/2 ml inj.

Mydriatics

Atropine is a potent mydriatic but its slow and long-lasting action is undesirable for refraction testing. Though the pupil dilates in 30–40 min, cycloplegia takes 1–3 hours, and the subject is visually handicapped for about a week. The substitutes attempt to overcome these difficulties.

1. *Homatropine* It is 10 times less potent than atropine. Instilled in the eye, it acts in 45–60 min, mydriasis lasts 1–3 days while accommodation recovers in 1–2 days. It often produces unsatisfactory cycloplegia in children who have high ciliary muscle tone.

HOMATROPINE EYE, HOMIDE 1%, 2% eye drops.

2. *Cyclopentolate* It is potent and rapidly acting; mydriasis and cycloplegia occur in 30–60 min and last about a day. It is preferred for cycloplegic refraction, but children may show transient behavioural abnormalities due to absorption of the drug after passage into the nasolacrimal duct. It is also used in iritis and uveitis.

CYCLOMID EYE 0.5%, 1%; CYCLOGYL, CYCLOPENT 1% eye drops.

3. *Tropicamide* It has the quickest (20–40 min) and briefest (3–6 hours) action, but is a relatively unreliable cycloplegic. However, it is satisfactory for refraction testing in adults and as a short acting mydriatic for fundoscopy. The mydriatic action can be augmented by combining with phenylephrine.

OPTIMIDE, TROPICAMET, TROMIDE 0.5%, 1.0% eye drops. TROPAC-P, TROPICAMET PLUS 0.8% with phenylephrine 5% eye drops.

Antiparkinsonian drugs (*see* Ch. 31)

USES

I. As antisecretory

1. *Preanaesthetic medication* When irritant general anaesthetics (ether) were used, prior administration of anticholinergics (atropine, hyoscine, glycopyrrolate) was imperative to check increased salivary and tracheobronchial secretions. However, with current use of nonirritating

anaesthetics (halothane, etc.) the requirement has decreased, though atropine may still be employed because halothane sensitizes the heart to NA mediated ventricular arrhythmias which are specially prone to occur during vagal slowing. Atropinic drugs also prevent laryngospasm, not by an action on laryngeal muscles, which are skeletal muscles, but by reducing respiratory secretions that reflexly predispose to laryngospasm. Vasovagal attack during anaesthesia can also be prevented.

2. *Peptic ulcer* Atropinic drugs decrease gastric secretion (fasting and neurogenic phase, but little effect on gastric phase) and afford symptomatic relief in peptic ulcer, though effective doses always produce side effects. They have now been superseded by H_2 blockers/proton pump inhibitors.

3. *Pulmonary embolism* These drugs benefit by reducing pulmonary secretions evoked reflexly by embolism.

4. To check excessive sweating or salivation, e.g. in parkinsonism.

II. As antispasmodic

1. Intestinal and renal colic, abdominal cramps: symptomatic relief is afforded if there is no mechanical obstruction. However, parenteral opioids and NSAIDs provide greater pain relief in renal colic than atropine. Atropine is less effective in biliary colic and is not able to completely counteract biliary spasm due to opiates (nitrates are more effective).
2. Nervous, functional and drug induced diarrhoea may be controlled to some extent, but anticholinergics are not useful in infective diarrhoea.
3. Spastic constipation, irritable bowel syndrome: modest symptomatic relief may be afforded.
4. Pylorospasm, gastric hypermotility, gastritis, nervous dyspepsia may be partially suppressed.
5. To relieve urinary frequency and urgency, enuresis in children. Oxybutynin, tolterodine and flavoxate have demonstrated good efficacy, but dry mouth and other anticholinergic effects are dose limiting.

6. Dysmenorrhoea: These drugs are not very effective; NSAIDs are superior.

III. Bronchial asthma, asthmatic bronchitis, COPD

Reflex vagal activity is an important factor in causing bronchoconstriction and increased secretion in chronic bronchitis and COPD, but to a lesser extent in bronchial asthma. Orally administered atropinic drugs are bronchodilators, but less effective than adrenergic drugs; not clinically used. They dry up secretion in the respiratory tract, may lead to its inspissation and plugging of bronchioles resulting in alveolar collapse and predisposition to infection. The mucociliary clearance is also impaired. Inhaled ipratropium bromide has been found to be specially effective in asthmatic bronchitis and COPD, though less so in bronchial asthma. Given by aerosol, it neither decreases respiratory secretions nor impairs mucociliary clearance, and there are few systemic side effects. Thus, it has a place in the management of COPD. Its time course of action makes it more suitable for regular prophylactic use rather than for control of acute attacks. The additive bronchodilator action with adrenergic drugs is utilized to afford relief in acute exacerbation of asthma/COPD by administering a combination of nebulized ipratropium and β_2 agonist through a mask.

Tiotropium bromide is an equally effective and longer acting alternative to ipratropium bromide.

IV. As mydriatic and cycloplegic

(i) *Diagnostic* For testing error of refraction, both mydriasis and cycloplegia are needed. Tropicamide having briefer action has now largely replaced homatropine for this purpose. These drugs do not cause sufficient cycloplegia in children: more potent agents like atropine or hyoscine have to be used. Atropine ointment (1%) applied 24 hours and 2 hours before is often preferred for children below 5 years. Cyclopentolate drops are an alternative.

To facilitate fundoscopy only mydriasis is needed; a short acting antimuscarinic may be used,

but phenylephrine is preferred, especially in the elderly, for fear of precipitating or aggravating glaucoma. A combination of phenylephrine + tropicamide drops is frequently used.

(ii) *Therapeutic*   Because of its long lasting mydriatic-cycloplegic and local anodyne (pain relieving) action on cornea, atropine is very valuable in the treatment of iritis, iridocyclitis, choroiditis, keratitis and corneal ulcer. It gives rest to the intraocular muscles and cuts down their painful spasm. Atropinic drugs alternated with a miotic prevent adhesions between iris and lens or iris and cornea and may even break them if already formed.

V. As cardiac vagolytic

Atropine is useful in counteracting sinus bradycardia and partial heart block in selected patients where increased vagal tone is responsible, e.g. in some cases of myocardial infarction and in digitalis toxicity. However, cardiac arrhythmias or ischaemia may be precipitated in some cases.

VI. For central action

1. *Parkinsonism* (*see* Ch. 31) Central anticholinergics are less effective than levodopa; They are used in mild cases, in drug induced extrapyramidal syndromes and as adjuvant to levodopa.

2. *Motion sickness*   Hyoscine is the most effective drug for motion sickness. It is particularly valuable in highly susceptible individuals and for vigorous motions. The drug should be given prophylactically (0.2 mg oral), because administration after symptoms have setin is less effective; action lasts 4–6 hours. A transdermal preparation applied behind the pinna 4 hours before journey has been shown to protect for 3 days. Side effects with low oral doses and transdermal medication are few, but dry mouth and sedation can occur: driving is risky. Dicyclomine is another anticholinergic used for motion sickness. These drugs are not effective in other types of vomiting.

3. Hyoscine was used to produce sedation and amnesia during labour (twilight sleep) and to control maniacal states. It had earned a reputation as a 'lie detector' during world war II: its amnesic and depressant action was believed to put the subject 'off guard' in the face of sustained interrogation and sleep deprivation, so that he came out with the truth.

VII. To antagonise muscarinic effects of drugs and poisons

Atropine is the specific antidote for anti ChE and early mushroom poisoning (*see* Ch. 7). Atropine or glycopyrrolate is also given to block muscarinic actions of neostigmine used for myasthenia gravis, decurarization or cobra envenomation.

SIDE EFFECTS AND TOXICITY

Side effects are quite common with the use of atropine and its congeners; are due to facets of its action other than for which it is being used. They cause inconvenience but are rarely serious.

Belladonna poisoning may occur due to drug overdose or consumption of seeds and berries of belladonna/datura plant. Children are highly susceptible. Manifestations are due to exaggerated pharmacological actions.

Dry mouth, difficulty in swallowing and talking. Dry, flushed and hot skin (especially over face and neck), fever, difficulty in micturition, decreased bowel sounds. A scarlet rash may appear. Dilated pupil, photophobia, blurring of near vision, palpitation.

Excitement, psychotic behaviour, ataxia, delirium, dreadful visual hallucinations.

Hypotension, weak and rapid pulse, cardiovascular collapse with respiratory depression. Convulsions and coma occur only in severe poisoning.

Diagnosis   Methacholine 5 mg or neostigmine 1 mg s.c. fails to induce typical muscarinic effects.

Treatment   If poison has been ingested, gastric lavage should be done with tannic acid ($KMnO_4$ is ineffective in oxidizing atropine). The patient should be kept in a dark quiet room. Cold sponging or ice bags are applied to reduce body temperature. Physostigmine 1–3 mg s.c. or i.v. antagonises both central and peripheral effects,

but has been found to produce hypotension and arrhythmias in some cases. As such, its utility is controversial. Neostigmine does not antagonise the central effects.

Other general measures (maintenance of blood volume, assisted respiration, diazepam to control convulsions) should be taken as appropriate.

Contraindications Atropinic drugs are absolutely contraindicated in individuals with a narrow iridocorneal angle—may precipitate acute congestive glaucoma. However, marked rise in intraocular tension is rare in patients with wide angle glaucoma.

Caution is advocated in elderly males with prostatic hypertrophy—urinary retention can occur.

Interactions

1. Absorption of most drugs is slowed because atropine delays gastric emptying. This results in slower absorption and greater peripheral degradation of levodopa—less of it reaches the brain. This does not occur when a peripheral decarboxylase inhibitor is combined.

   On the other hand, extent of digoxin and tetracycline absorption may be increased due to longer transit time in the g.i.t.
2. Antacids interfere with absorption of anticholinergics.
3. Antihistaminics, tricyclic antidepressants, phenothiazines, disopyramide, pethidine have anticholinergic property—additive side effects occur with atropinic drugs.
4. MAO inhibitors interfere with metabolism of anticholinergic antiparkinsonian drugs — delirium may occur.

DRUGS ACTING ON AUTONOMIC GANGLIA

Acetylcholine is the primary excitatory neurotransmitter in both sympathetic and parasympathetic ganglia. Drugs which inhibit synthesis (hemicholinium) or release (botulinum toxin, procaine) of ACh can interfere with ganglionic transmission, but drugs which act on cholinergic receptors in the ganglia are more selective.

In addition to the dominant nicotinic N_N receptors, which mediate the primary rapid depolarization of ganglionic cells, there are subsidiary muscarinic M_1, M_2, adrenergic, dopaminergic, amino acid and peptidergic receptors which bring about secondary, slowly developing but longer lasting changes in membrane potential, both positive and negative, that modulate the primary response. Separate catecholamine (NA, DA) and amino acid transmitter containing cells are present in ganglia, but peptides are released from the preganglionic cholinergic terminals themselves. Thus, autonomic ganglion is not merely a one transmitter—one cell junction, but a complex system capable of local adjustments in the level of excitability.

Drugs can either stimulate or block the ganglia.

GANGLIONIC STIMULANTS

Selective nicotinic agonists	*Nonselective/ muscarinic agonists*
Nicotine (small dose)	Acetylcholine
Lobeline	Carbachol
Dimethyl phenyl piperazinium (DMPP)	Pilocarpine
Tetramethyl ammonium (TMA)	Anticholinesterases
	MCN 343-A
Varenicline	

Nicotine

It is the principal alkaloid in tobacco (*Nicotiana tabacum*); acts as an agonist on both N_N and N_M subtypes of nicotinic cholinergic receptors (NRs). Sympathetic as well as parasympathetic ganglia are stimulated, but larger doses cause persistent depolarization and ganglionic blockade. Nicotine is important in the context of smoking and tobacco chewing; its only clinical indication is short-term nicotine replacement in tobacco abstinent subjects. There is no therapeutic application of ganglionic stimulants, because no useful purpose can be served by stimulating both sympathetic and parasympathetic ganglia concurrently.

Treatment of smoking cessation/quiting tobacco chewing

Majority of smokers (and tobacco chewers) wish to quit smoking/chewing, but fail to do so because of nicotine dependence. The most important measure to help smokers quit is counselling and motivation. This may be supplemented by pharmacotherapy. The goals of such pharmacotherapy are:

- To reduce the craving for the satisfying (reward) effects of nicotine.
- To suppress the physical withdrawal symptoms of nicotine.

The drugs currently utilized for the above goals are:

- Nicotine replacement
- Partial agonists of $\alpha 4\beta 2$ NRs (Varenicline)
- Antidepressants (Bupropion)

Nicotine transdermal This patch formulation of nicotine is applied once daily on the hip/abdomen/chest/upper arm as an aid to smoking cessation. It ameliorates the symptoms of nicotine withdrawal, but only partially suppresses the craving, because the intermittent peak nicotine blood levels that occur during smoking are not reproduced by the patch.

NICOTINELL-TTS 10, 20, 30 cm^2 patches releasing 7, 14, 21 mg nicotine per 24 hr respectively. in those smoking > 20 cigarettes every day-start with 30 cm^2 patch, shift to smaller patches every 5–8 days, treat for 3–4 weeks (max. 12 weeks).

Nicotine chewing gum Developed as an alternative to nicotine transdermal, this formulation is found more satisfying by some dependent subjects. The number of gum pieces chewed daily can be adjusted according to the need felt.

NULIFE 1, 2, 4 mg chewing gum; for those smoking >20 cigarettes/day—start with 4 mg gum chewed and retained in mouth for 30 min when urge to smoke is felt. After a few days change over to 2 mg gum and then to 1 mg gum. Not more than 15 pieces to be used in a day. Treatment can be started at lower doses for less heavy smokers.
A nasal spray delivering 0.5 mg per activation, and an inhaler with nicotine cartridge are also available in some countries.

Side effects of nicotine replacement therapy are headache, dyspepsia, abdominal cramps, loose motions, insomnia, flu-like symptoms and local irritation. Vasospastic angina may be precipitated. Cardiac arrhythmias and ischaemic heart disease are the contraindications.

Varenicline This $\alpha 4\beta 2$ subtype NR selective partial agonist has been marketed as oral tablets in many countries (UK, USA, Europe, etc) to help smoking cessation. Recent evidence has shown that the reward (reinforcing) action of nicotine is exerted through the $\alpha 4\beta 2$ subtype of neuronal NRs which are mainly localized in nucleus accumbens and other mesolimbic areas. Activation of these NRs by nicotine induces DA release which produces feelings of satisfaction/reward and has reinforcing effect. Since varenicline is a partial agonist at these receptors, it provides some level of nicotine substitution, but blocks the reward effect of smoking. Clinically it has been found to reduce craving as well as nicotine withdrawal symptoms in those who stop smoking. Abstinence rates at one year of cessation are comparable to those of nicotine replacement and of bupropion. However, varenicline is not entirely safe. Side effects noted are mood changes, irrational behaviour, appetite and taste disturbances, sleep disorder and agitation. Warning has been issued that it may promote suicidal thoughts.

Dose: Initially 0.5 mg OD, gradually increase upto 1 mg BD according to need, for not more than 12 weeks; then taper off.

Bupropion This atypical antidepressant inhibits reuptake of DA and NA, and has been marketed as a sustained release tablet specifically for smoking cessation. Clinical efficacy has been rated equivalent to nicotine replacement, and it has produced fewer side effects (*see* Ch. 33).

GANGLION BLOCKING AGENTS

A. *Competitive blockers*
   Quaternary ammonium compounds
      Hexamethonium, Pentolinium

TABLE 8.2   Relative autonomic tone and effects of ganglionic blockade on organ function

Organ	Dominant tone	Effect of ganglionic blockade (Side effect)
1. Heart	Para-symp.	Tachycardia (palpitation)
2. Blood vessels	Symp.	Vasodilatation, abolition of reflexes (postural and exercise hypotension, syncope)
3. Iris	Para-symp.	Mydriasis (photophobia)
4. Ciliary muscle	Para-symp.	Cycloplegia (blurring of near vision)
5. Intestines	Para-symp.	Decreased motility (distension, constipation)
6. Bladder	Para-symp.	Decreased tone (difficulty in micturition)
7. Male sexual function	Para-symp. Symp.	Inhibition of erection Inhibition of ejaculation } (impotence)
8. Salivary glands	Para-symp.	Inhibition of salivation (dryness of mouth, difficulty in swallowing and talking)
9. Sweat glands	Symp. (cholinergic)	Inhibition of sweating (anhydrosis)

Amines (secondary/tertiary)
Mecamylamine, Pempidine

Monosulfonium compound
Trimethaphan camforsulfonate

B. *Persistent depolarising blockers*
Nicotine (large dose)
Anticholinesterases (large dose)

The competitive ganglion blockers were used in the 1950s for hypertension and peptic ulcer, but have been totally replaced now because they produce a number of intolerable side effects (*see* Table 8.2). In fact, these side effects help in understanding the relative roles of sympathetic and parasympathetic divisions in regulating the various organ functions.

Trimethaphan   It is an ultrashort acting ganglion blocker; has been occasionally infused i.v. to produce controlled hypotension and in hypertensive emergency due to aortic dissection.

Mecamylamine Either alone or in combination with nicotine patch, it has been tried for smoking cessation. It appears to block the reward effect of nicotine and improve abstinence rate compared to placebo. Constipation occurred in many subjects, and it is not an approved drug.

There is at present no clinical relevance of ganglion blockers.

☞ **PROBLEM DIRECTED STUDY**

8.1 An elderly male aged 74 years was brought to the hospital since he had not passed urine for the past 24 hours and had severe pain in lower abdomen. On examination there was a bulge in the pubic region due to full urinary bladder. On catheterization, he passed 1.5L urine and the pain was relieved.

He gave the history of having difficulty in passing urine, poor stream, frequent urge to urinate and post-void dribbling for the last 3 years. Over the past few days he had been experiencing episodes of vertigo for which he was prescribed a medicine that he was taking for 2 days. Examination of the prescription revealed that he was taking tab. Dimenhydrinate 50 mg 3 times daily.
(a) Could there be any relationship between the anti-vertigo medication and the episode of acute urinary retention?
(see Appendix-1 for solution)

Chapter 9 Adrenergic System and Drugs

ADRENERGIC TRANSMISSION

Adrenergic (more precisely 'Noradrenergic') transmission is restricted to the sympathetic division of the ANS. There are three closely related endogenous catecholamines (CAs).

Noradrenaline (NA)   It acts as transmitter at postganglionic sympathetic sites (except sweat glands, hair follicles and some vasodilator fibres) and in certain areas of brain.

Adrenaline (Adr)   It is secreted by adrenal medulla and may have a transmitter role in the brain.

Dopamine (DA)   It is a major transmitter in basal ganglia, limbic system, CTZ, anterior pituitary, etc. and in a limited manner in the periphery.

1. Synthesis of CAs   Catecholamines are synthesized from the amino acid phenylalanine as depicted in Fig. 9.1. Tyrosine hydroxylase is a specific and the rate limiting enzyme. Its inhibition by α-methyl-p-tyrosine results in depletion of CAs. This inhibitor can be used in pheochromocytoma before surgery and in inoperable cases. All other enzymes of CA synthesis are rather nonspecific and can act on closely related substrates, e.g. dopa decarboxylase can form 5-HT from 5-hydroxytryptophan and α methyl DA from α methyl dopa. Synthesis of NA occurs in all adrenergic neurones, while that of Adr occurs only in the adrenal medullary cells. It requires high concentration of glucocorticoids reaching through the intraadrenal portal circulation for induction of the methylating enzyme.

2. Storage of CAs   NA is stored in synaptic vesicles or 'granules' within the adrenergic nerve terminal (Fig. 9.4). The vesicular membrane
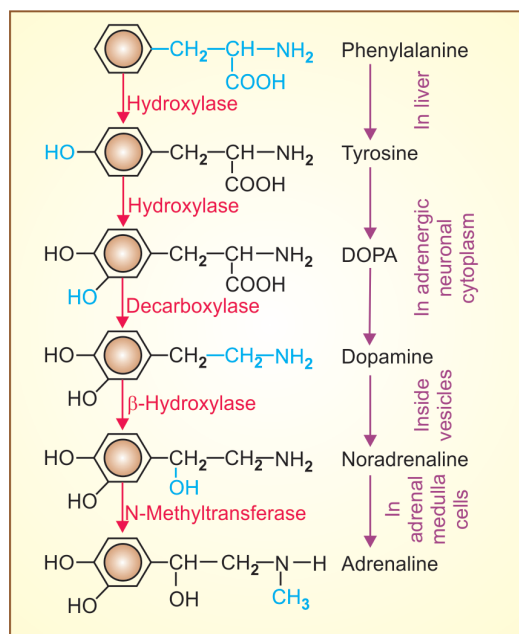
Fig. 9.1: Steps in the synthesis of catecholamines

actively takes up DA from the cytoplasm and the final step of synthesis of NA takes place inside the vesicle which contains dopamine β-hydroxylase. NA is then stored as a complex with ATP (in a ratio of 4 : 1) which is adsorbed on a protein *chromogranin*. In the adrenal medulla the NA thus formed within the chromaffin granules diffuses out into the cytoplasm, is methylated and Adr so formed is again taken up by a separate set of granules. The cytoplasmic pool of CAs is kept low by the enzyme monoamine oxidase (MAO) present on the outer surface of mitochondria.

3. Release of CAs The nerve impulse coupled release of CA takes place by *exocytosis* (*see* p. 95) and all the vesicular contents (NA or Adr, ATP, dopamine β hydroxylase, chromogranin) are

poured out. In case of vesicles which in addition contain peptides like enkephalin or neuropeptide Y (NPY), these cotransmitters are simultaneously released. The release is modulated by presynaptic receptors, of which α_2 inhibitory control is dominant.

The autoreceptors of other cotransmitters (Y_2 of NPY and P1 of ATP) also inhibit transmitter release. In addition, numerous heteroreceptors are expressed on the adrenergic neurone which either inhibit (dopaminergic, serotonergic, muscarinic and PGE_2) or enhance (β_2 adrenergic, angiotensin AT_1 and nicotinic) NA release.

Indirectly acting sympathomimetic amines (tyramine, etc.) also induce release of NA, but they do so by displacing NA from the nerve ending binding sites and by exchange diffusion utilizing norepinephrine transporter (NET) the carrier of uptake-1 (*see* below). This process is not exocytotic and does not require Ca^{2+}.

4. Uptake of CAs There is a very efficient mechanism by which NA released from the nerve terminal is recaptured. This occurs in 2 steps—

Axonal uptake An active amine pump (NET) is present at the neuronal membrane which transports NA by a Na^+ coupled mechanism. It takes up NA at a higher rate than Adr and had been labelled *uptake-1*. The indirectly acting sympathomimetic amines like tyramine, but not isoprenaline, also utilize this pump for entering the neurone. This uptake is the most important mechanism for terminating the postjunctional action of NA. From 75% to 90% of released NA is retaken back into the neurone. This pump is inhibited by cocaine, desipramine and few other drugs.

Vesicular uptake The membrane of intracellular vesicles has another amine pump the 'vesicular monoamine transporter' (VMAT-2), which transports CA from the cytoplasm to the interior of the storage vesicle. The VMAT-2 transports monoamines by exchanging with H^+ ions. The vesicular NA is constantly leaking out into the axoplasm and is recaptured by this mechanism. This carrier also takes up DA formed in the axoplasm for further synthesis to NA. Thus, it is very important in maintaining the NA content

of the neurone. This uptake is inhibited by reserpine, resulting in depletion of CAs.

Extraneuronal uptake of CAs (uptake-2) is carried out by extraneuronal amine transporter (ENT or OCT3) and other organic cation transporters OCT1 and OCT2 into cells of other tissues. In contrast to NET this uptake transports Adr at a higher rate than NA, is not Na^+ dependent and is not inhibited by cocaine, but inhibited by corticosterone. It may capture circulating Adr, but is quantitatively minor and not of physiological or pharmacological importance.

5. Metabolism of CAs The pathways of metabolism of CAs are depicted in Fig. 9.2. Part of the NA leaking out from vesicles into cytoplasm as well as that taken up by axonal transport is first attacked by MAO, while that which diffuses into circulation is first acted upon by catechol-o-methyl transferase (COMT) in liver and other tissues. In both cases, the alternative enzyme can subsequently act to produce vanillylmandelic acid (VMA). Other intermediate step enzymes involved are aldehyde reductase (AR), aldehyde dehydrogenase (AD) and alcohol dehydrogenase (ADH). The major metabolites excreted in urine are VMA and 3-methoxy-4-hydroxy phenyl glycol (a reduced product) along with some metanephrine, normetanephrine and 3,4 dihydroxy mandelic acid. These metabolites are mostly conjugated with glucuronic acid or sulfate before excretion in urine. Only 25–50 μg of NA and 2–5 μg of Adr are excreted in the free form in 24 hours. However, metabolism does not play an important role in terminating the action of neuronally released CAs.

6. Adrenergic receptors Adrenergic receptors are membrane bound G-protein coupled receptors which function primarily by increasing or decreasing the intracellular production of second messengers cAMP or IP_3/DAG. In some cases the activated G-protein itself operates K^+ or Ca^{2+} channels, or increases prostaglandin production.

Ahlquist (1948), on the basis of two distinct rank order of potencies of adrenergic agonists
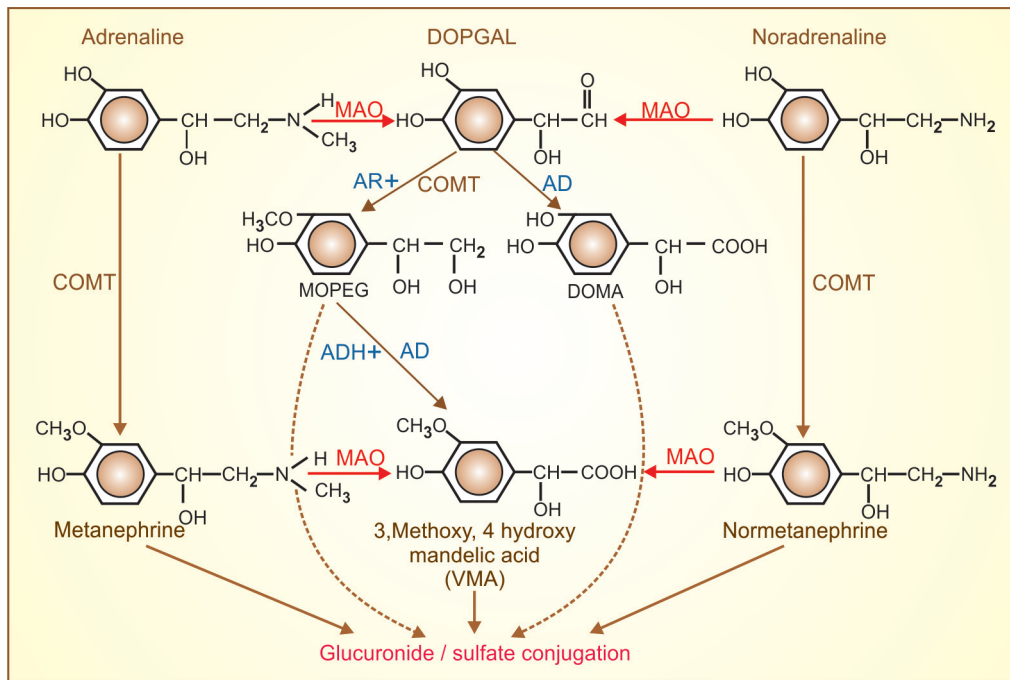
Fig. 9.2: Metabolism of catecholamines

MAO—Monoamine oxidase; COMT—Catechol-O-methyl transferase; AR—Aldehyde reductase; AD—Aldehyde dehydrogenase; ADH—Alcohol dehydrogenase; DOMA—3,4 dihydroxy mandelic acid; MOPEG—3-methoxy, 4-hydroxy phenyl glycol; VMA—vanillyl mandelic acid.

(Fig. 9.3), classified adrenergic receptors into two types α and β. This classification was confirmed later by the discovery of selective α and β adrenergic antagonists. Important features of α and β receptors are given in Table 9.1.

On the basis of relative organ specificity of selective agonists and antagonists the β receptors were further subdivided into β_1 and β_2 subtypes. Later, β_3 (atypical β) receptors were described which are more sensitive to NA than to Adr, and

Fig. 9.3: Dose-response curves of 3 catecholamines adrenaline (Adr), noradrenaline (NA) and isoprenaline (Iso) on isolated aortic strip and isolated bronchial smooth muscle illustrating two distinct rank orders of potencies respectively for α and β adrenergic receptors

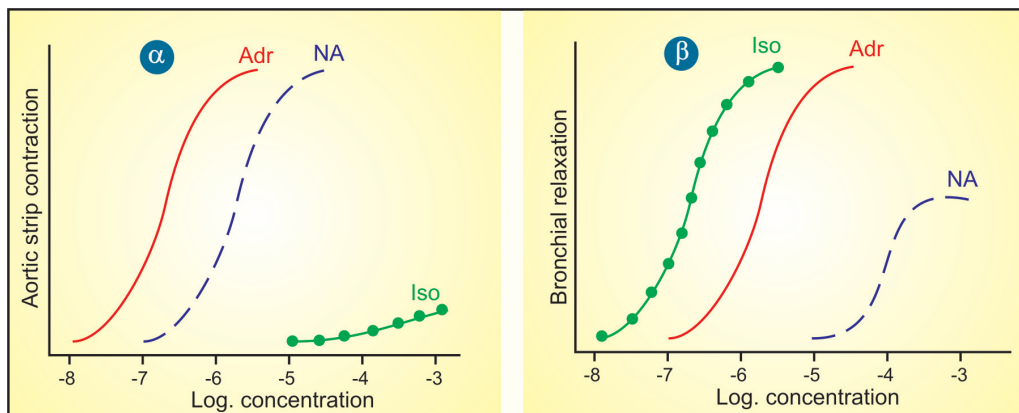| TABLE 9.1	Differences between α and β adrenergic receptors	
	α	β
1. Rank order of potency of agonists	*Adr $\geq$ NA > Iso	Iso > Adr > NA
2. Antagonist	Phenoxybenzamine	Propranolol
3. Coupling protein	Gq/Gi/Go	Gs
4. Effector pathway	IP_3/DAG↑, cAMP ↓, K^+ channel ↑	cAMP↑, Ca^{2+} channel ↑

* Though inherently NA is equipotent to Adr on α receptors, in test systems with intact neuronal reuptake, it appears less potent due to faster reuptake.

TABLE 9.2	Differences between β_1, β_2 and β_3 receptors		
	β_1	β_2	β_3
1. Location	Heart, JG cells in kidney	Bronchi, blood vessels, uterus, liver, g.i.t., urinary tract, eye	Adipose tissue
2. Selective agonist	Dobutamine	Salbutamol, terbutalin	BRL 37344
3. Selective antagonist	Metoprolol, Atenolol	ICI 118551 α-methyl propranolol	CGP 20712A (also β_1) ICI 118551 (also β_2)
4 Relative potency of NA and Adr	NA $\leq$ Adr	NA << Adr	NA > Adr

TABLE 9.3	Differences between α_1 and α_2 receptors	
	α_1	α_2
Location	Postjunctional on effector organs	Prejunctional on nerve ending (α_{2A}), also postjunctional in brain, pancreatic β cells and extrajunctional in certain blood vessels, platelets
Function subserved	GU Smooth muscle–contraction Vasoconstriction Gland—secretion Gut—relaxation Liver—glycogenolysis Heart—arrhythmia	Inhibition of transmitter release Vasoconstriction Decreased central sympathetic flow Decreased insulin release Platelet aggregation
Selective agonist	Phenylephrine, Methoxamine	Clonidine
Selective antagonist	Prazosin	Yohimbine, Rauwolscine
Coupling protein	Gq	Gi/Go
Effector pathway	IP_3/DAG ↑ Phospholipase A_2 ↑—PG release	cAMP ↓ K^+ channel ↑ Ca^{2+} channel ↓ or ↑ IP_3/DAG ↑

GU: Genitourinary

have very low affinity for the standard β blockers. These are located on adipocytes, mediate lipolysis and induce thermogenesis. Selective β_3 agonists have the potential to be used as antiobesity drugs.

In the mid 1970s the α receptors were demonstrated to be present prejunctionally as well. To differentiate these release inhibitory prejunctional α receptors, a subdivision into α_1 and α_2 was suggested. However, the present classification into α_1 and α_2 is based on pharmacological criteria (selectivity of agonists and antagonists) and not on anatomical location. Molecular cloning has further identified 3 subtypes of α_1 (α_{1A}, α_{1B}, α_{1D}) and 3 subtypes of α_2 (α_{2A}, α_{2B}, α_{2C}) receptors.

Though tissue distribution of subtypes of α_1 and α_2 receptors has been mapped, there is lot of overlap. Sufficiently subtype selective agonists or antagonists have also not yet been developed to pharmacologically exploit the molecular heterogeneity of subtypes of α_1 and α_2 receptors.

The adrenergic neuronal mechanisms and action of drugs which modify them are depicted in Fig. 9.4. A summary of drugs acting through adrenergic neuronal mechanisms is presented in Table 9.4
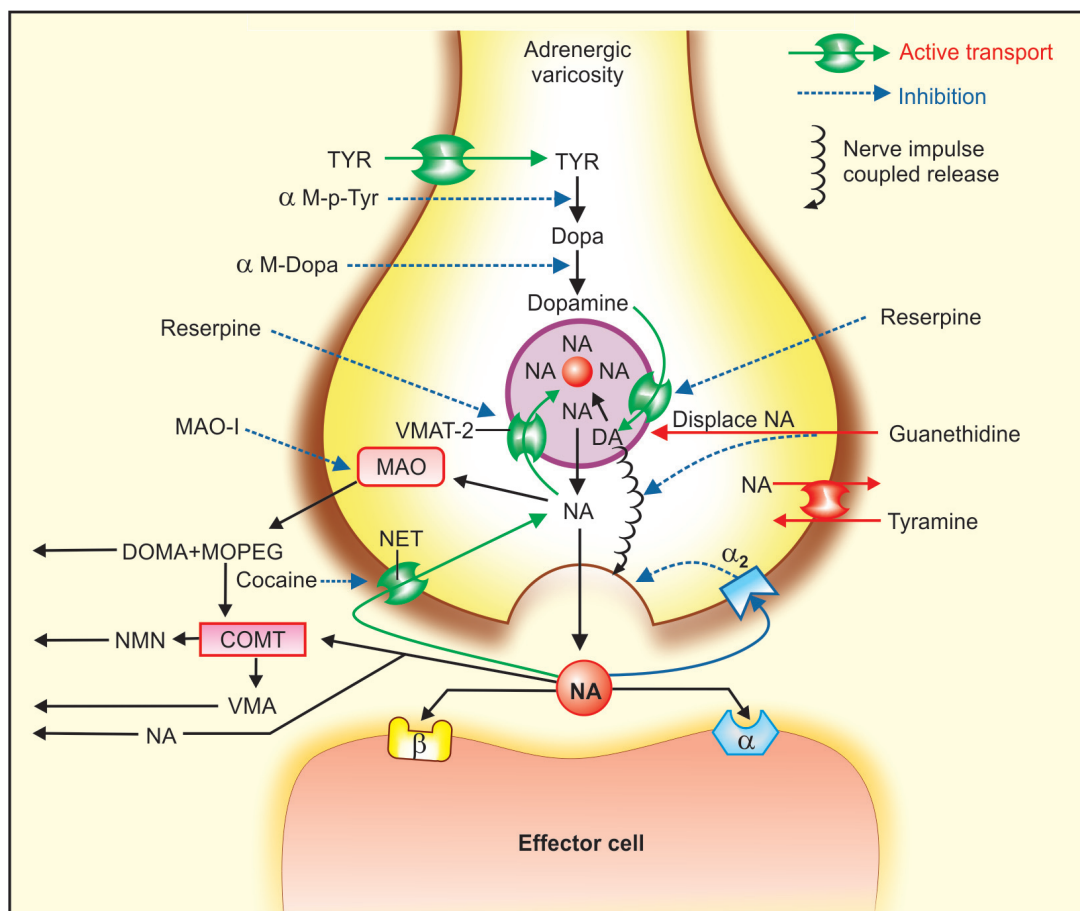
Fig. 9.4: Schematic representation of adrenergic neurotransmission and its modification by drugs
TYR—tyrosine; α M-p-Tyr—α methyl-p-tyrosine; α M-Dopa—α methyl dopa; MAO—monoamine oxidase; MAOI—monoamine oxidase inhibitor; COMT—catechol-o-methyl transferase; NMN—nor-metanephrine; VMA—vanillyl mandelic acid; NET—Norepinephrine transporter; VMAT-2—Vesicular monoamine transporter; DOMA—3,4 dihydroxy mandelic acid; MOPEG—3-Methoxy,4-hydroxy phenyl glycol.

	Step/site	Action	Drug	Response
1.	Synthesis of NA	Inhibition Utilisation of same synthetic pathway	α-methyl-p-tyrosine α-methyl dopa	Depletion of NA Replacement of NA by a-methyl NA (false transmitter)
2.	Axonal uptake	Blockade	Cocaine, desipramine, guanethidine, ephedrine	Potentiation of NA (endo-and exogenous), inhibition of tyramine
3.	Vesicular uptake	Blockade	Reserpine	Depletion of NA (degraded by MAO)
4.	Nerve impulse coupled release of NA	Inhibition	Guanethidine, bretylium	Loss of transmission
5.	Vesicular NA	Displacement	Guanethidine	Initially sympathomimetic, depletion of NA later
6.	Membrane NA pool	Exchange diffusion	Tyramine, ephedrine	Indirect sympathomimetic
7.	Metabolism	MAO-inhibition	Nialamide, tranylcypromine	Potentiation of NA (slight), —of tyramine (marked)
		MAO-A inhibition	Moclobemide	Potentiation of NA and tyramine (slight)
		MAO-B inhibition COMT inhibition	Selegiline Tolcapone, entacapone	Potentiation of DA in brain Potentiation of NA and DA (slight)
8.	Receptors	Mimicking	Phenylephrine Clonidine	α_1 sympathomimetic α_2–inhibition of NA release, ↓ sympathetic outflow
			Isoprenaline Dobutamine	$\beta_1 + \beta_2$ —sympathomimetic β_1—sympathomimetic: cardiac stimulation
			Salbutamol	β_2—sympathomimetic: bronchodilatation
		Blockade	Phenoxybenzamine Prazosin Yohimbine Propranolol Metoprolol	$\alpha_1 + \alpha_2$—blockade α_1—blockade α_2—blockade $\beta_1 + \beta_2$—blockade β_1—blockade

TABLE 9.4 Summary of drug action through modification of adrenergic transmission

CHAPTER 9

ADRENERGIC DRUGS (Sympathomimetics)

These are drugs with actions similar to that of Adr or of sympathetic stimulation.

Direct sympathomimetics They act directly as agonists on α and/or β adrenoceptors—Adr, NA, isoprenaline (Iso), phenylephrine, methoxamine, xylometazoline, salbutamol and many others.

Indirect sympathomimetics They act on adrenergic neurone to release NA, which then acts on the adrenoceptors—tyramine, amphetamine.

Mixed action sympathomimetics They act directly as well as indirectly—ephedrine, dopamine, mephentermine.

ACTIONS

The peripheral actions of Adr in most tissues

SECTION 2

TABLE 9.5	Adrenergic responses mediated through α and β receptors
α actions	**β actions**
1. Constriction of arterioles and veins → rise inBP ($\alpha_1 + \alpha_2$)	Dilatation of arterioles and veins → fall in BP (β_2)
2. Heart—little action, arrhythmia at high dose (α_1)	Cardiac stimulation (β_1), ↑ rate, force and conduction velocity
3. —	Bronchodilatation (β_2)
4. Contraction of radial muscles of iris → mydriasis (α_1), decreased aqueous secretion	No effect on iris, slight relaxation of ciliary muscle, Enhanced aqueous secretion
5. Intestinal relaxation, contraction of sphincters	Intestinal relaxation (β_2)
6. Bladder trigone—contraction (α_1)	Detrusor—relaxation (β_2)
7. Uterus—contraction (α_1)	Relaxation (β_2)
8. Splenic capsule—contraction (α_1)	Relaxation (β_2) (slight)
9. Neuromuscular transmission facilitated, ↑ ACh release	Active state—prolonged in fast contracting muscle, abbreviated in slow contracting muscle; tremors (β_2)
10. Insulin secretion inhibited (α_2) (dominant)	Augmented insulin (mild) and glucagon secretion (β_2)
11. Liver—glycogenolysis (α in some species)	Liver—glycogenolysis (β_2) → hyperglycaemia Muscle—glycogenolysis (β_2) → hyperlactacidaemia Fat—lipolysis ($\beta_1 + \beta_2 + \beta_3$) → increased blood FFA, calorigenesis
12. —	Renin release from kidney (β_1)
13. Male sex organs—ejaculation (α_1)	—
14. Salivary gland—K$^+$ and water secretion (α_1)	Ptylin secretion
15. —	ADH secretion from posterior pituitary (β_1)
16. Nictitating membrane—contraction (in animals)	—

have been clearly differentiated into those mediated by α or β receptors depending on the predominant receptor type present in a given tissue. These are tabulated in Table 9.5. The receptor subtype, wherever defined, has been mentioned in parenthesis. The actions of a particular sympathomimetic amine depend on its relative activity at different types of adrenergic receptors.

Adr : $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak β_3 action
NA : $\alpha_1 + \alpha_2 + \beta_1 + \beta_3$ but no β_2 action
Iso : $\beta_1 + \beta_2 + \beta_3$ but no α action

Important actions of Adr, NA and isoprenaline are compared in Table 9.6.

The overall actions are—

1. Heart   Adr increases heart rate by increasing the slope of slow diastolic depolarization of cells in the SA node. It also activates latent pacemakers in A-V node and Purkinje fibres; arrhythmias can occur with high doses that raise BP markedly. Raised BP reflexly depresses the SA node and unmasks the latent pacemakers. Certain anaesthetics (chloroform, halothane) sensitize the heart to arrhythmic action of Adr. Idioventricular rate is increased in patients with complete heart block.

Force of cardiac contraction is increased. Development of tension as well as relaxation are accelerated. Thus, systole is shortened more than diastole. Cardiac output and oxygen consumption of the heart are markedly enhanced.

Conduction velocity through A-V node, bundle of His, atrial and ventricular fibres is increased; partial A-V block may be overcome. Refractory

TABLE 9.6	Comparative effects of intravenous infusion of adrenaline, noradrenaline and isoprenaline		
	Adr	*NA*	*Iso*
1. Heart rate	↑	↓	↑↑
2. Cardiac output	↑↑	–	↑↑
3. BP—Systolic	↑↑	↑↑	↑
Diastolic	↓↑	↑↑	↓↓
Mean	↑	↑↑	↓
4. Blood flow			
Skin and mm	↓	↓	–
Sk. muscle	↑↑	–, ↓	↑
Kidney	↓	↓	–
Liver	↑↑	–	↑
Coronary	↑	↑	↑
5. Bronchial muscle	↓↓	–	↓↓
6. Intestinal muscle	↓↓	↓	↓
7. Blood sugar	↑↑	–, ↑	↑

period (RP) of all types of cardiac cells is reduced. All cardiac actions are predominantly β_1 receptor mediated.

When BP rises markedly, reflex bradycardia occurs due to stimulation of vagus— this is the usual response seen when NA is injected i.v.

2. Blood vessels Both vasoconstriction (α) and vasodilatation (β_2) can occur depending on the drug, its dose and vascular bed. Constriction predominates in cutaneous, mucous membrane and renal beds. Vasoconstriction occurs through both α_1 and α_2 receptors. However, location of α_2 (extrajunctional) receptors is such that they are activated only by circulating CAs, whereas α_1 (junctional) receptors primarily mediate responses to neuronally released NA. Dilatation predominates in skeletal muscles, liver and coronaries. The direct effect on cerebral vessels is not prominent—blood flow through this bed parallels change in BP.

The action is most marked on arterioles and precapillary sphincters; larger arteries and veins are affected at higher doses.

3. BP The effect depends on the amine, its dose and rate of administration.
- NA causes rise in systolic, diastolic and mean BP; it does not cause vasodilatation (no β_2 action), peripheral resistance increases consistently due to α action.
- Isoprenaline causes rise in systolic but marked fall in diastolic BP (β_1—cardiac stimulation, β_2— vasodilatation). The mean BP generally falls.
- Adr given by slow i.v. infusion or s.c. injection causes rise in systolic but fall in diastolic BP; peripheral resistance decreases because vascular β_2 receptors are more sensitive than α receptors. Mean BP generally rises. Pulse pressure is increased.
- Rapid i.v. injection of Adr (in animals) produces a marked increase in both systolic as well as diastolic BP (at high concentration α response predominates and vasoconstriction occurs even in skeletal muscles). The BP returns to normal within a few minutes and a secondary fall in mean BP follows. The mechanism is—rapid uptake and dissipation of Adr $\rightarrow$ concentration around the receptor is reduced $\rightarrow$ low concentrations are not able to act on α receptors but continue to act on β_2 receptors.

When an α blocker has been given, only fall in BP is seen—*vasomotor reversal of Dale.*

4. Respiration Adr and isoprenaline, but not NA are potent bronchodilators (β_2). This action

is more marked when the bronchi are constricted. Adr given by aerosol additionally decongests bronchial mucosa by α action. Adr can directly stimulate respiratory centre (RC) but this action is seldom manifest at clinically used doses. Rapid i.v. injection (in animals) causes transient apnoea due to reflex inhibition of RC. Toxic doses of Adr cause pulmonary edema by shifting blood from systemic to pulmonary circuit.

5. Eye   Mydriasis occurs due to contraction of radial muscles of iris (α_1), but this is minimal after topical application, because Adr penetrates cornea poorly. The intraocular tension tends to fall, especially in wide angle glaucoma.

Adr has complex effects on aqueous humor dynamics (*see* p. 154).

Action of adrenaline on aqueous humor dynamics	
Receptor	*Agonist action*
α_1 :	Vasoconstriction of ciliary vessels $\rightarrow$ reduced aqueous formation
α_2 :	Reduced secretory activity of ciliary epithelium
$?\alpha$:	Augmentation of uveo-scleral outflow
β_2 :	Enhanced secretory activity of ciliary epithelium
	Facilitation of trabecular outflow

Overall, aqueous formation is reduced and outflow is facilitated.

6. GIT   In isolated preparations of gut, relaxation occurs through activation of both α and β receptors. In intact animals and man peristalsis is reduced and sphincters are constricted, but the effects are brief and of no clinical import.

7. Bladder   Detrusor is relaxed (β) and trigone is constricted (α): both actions tend to hinder micturition.

8. Uterus   Adr can both contract and relax uterine muscle, respectively through α and β receptors. The overall effect varies with species, hormonal and gestational status. Human uterus is relaxed by Adr at term of pregnancy, but at other times, its concentrations are enhanced.

9. Splenic capsule   Contracts (α) and more RBCs are poured in circulation. This action is not evident in man.

10. Skeletal muscle   Neuromuscular transmission is facilitated. In contrast to action on autonomic nerve endings, α receptor activation on motor nerve endings augments ACh release, probably because it is of the α_1 subtype. The direct effect on muscle fibres is exerted through β_2 receptors and differs according to the type of fibre. The active state is abbreviated and less tension is developed in the slow contracting red fibres. There is incomplete fusion of individual responses. This along with enhanced firing of muscle spindles is responsible for the tremors produced by β_2 agonists. The action on rapidly contracting white fibres is to prolong the active state and increase the tension developed.

11. CNS   Adr, in clinically used doses, does not produce any marked CNS effects because of poor penetration in brain, but restlessness, apprehension and tremor may occur. Activation of α_2 receptors in the brainstem (by selective α_2 agonists) results in decreased sympathetic outflow $\rightarrow$ fall in BP and bradycardia.

12. Metabolic   Adr causes glycogenolysis $\rightarrow$ hyperglycaemia, hyperlactacidaemia (β_2); lipolysis $\rightarrow$ rise in plasma free fatty acid (FFA) and calorigenesis ($\beta_2 + \beta_3$). These are due to direct action on liver, muscle and adipose tissue cells. In addition metabolic effects result from reduction of insulin (α_2) and augmentation of glucagon (β_2) secretion.

Transient hyperkalaemia followed by hypokalaemia occurs due to initial release of K^+ from liver, and later its enhanced uptake into skeletal muscles as well as in liver.

Biochemical mediation of adrenergic responses

β *actions*   The β actions are mediated through cAMP (*see* Fig. 4.6). Adr activates membrane bound enzyme *adenylyl cyclase* through a regulatory protein Gs $\rightarrow$ ATP is broken down to cAMP at the inner face. This in turn phosphorylates a number of intracellular cAMP-dependent protein kinases and initiates a series of reactions:
(i) In *liver* and *muscle*, glycogen phosphorylase is activated causing glycogenolysis while glycogen synthase is inhibited. Both actions result in hyperglycaemia and hyperlactacidemia. Neoglucogenesis in liver adds to the response.

K^+ is first released from liver $\rightarrow$ hyperkalaemia; followed by more prolonged hypokalaemia due to K^+ uptake in muscle and later in liver itself.

(ii) In *adipose tissue,* triglyceride lipase is activated → increased plasma free fatty acids. Increased O_2 consumption and heat production result primarily by action on brown adipose tissue, which has predominant β_3 receptors.

(iii) In *heart,* proteins like troponin and phospholamban are phosphorylated. The former results in increased interaction with Ca^{2+} at the myofilaments → increased force of contraction; the latter causes sequestration of Ca^{2+} by sarcoplasmic reticulum → more rapid relaxation. The activated protein Gs, in addition, interacts directly with the Ca^{2+} channels in the membrane promoting influx of Ca^{2+} which reinforces the positive inotropic action exerted through cAMP.

(iv) In the *gut* and *bronchial muscle,* relaxation (accompanied with hyperpolarization) is induced, but the intermediate steps have not been clearly delineated.

(v) In *pancreatic islets* activation of β_2 receptors on α cells increases glucagon secretion, and that on β cells increases insulin secretion, both by raising intracellular cAMP. However, augmentation of insulin secretion is weak.

α actions The mediation of α actions is varied and less well defined.

(i) In *smooth muscles* (including vascular) that are contracted through α_1 receptors, the activated Gq-protein increases IP_3/DAG production → mobilization of Ca^{2+} from intracellular organelle → activation of calmodulin dependent myosin light chain kinase → phosphorylation of myosin → contraction. The vasoconstrictor α_2 receptors probably enhance Ca^{2+} influx without utilizing IP_3.

(ii) The *prejunctional* α_2 receptor appears to inhibit neuronal Ca^{2+} channels and also limit the intracellular availability of Ca^{2+} by decreasing cAMP production. Transmitter (NA) release is consequently diminished. Hyperpolarization through activation of G-protein gated K^+ channels may also occur.

(iii) In the *gut,* α_2 receptor activation hyperpolarizes the cholinergic neurone → decreased release of ACh → reduced tone; whereas α_1 receptors located directly on the smooth muscle cell increase K^+ efflux indirectly (by activating Ca^{2+} dependent K^+ channels) leading to hyperpolarization → relaxation.

(iv) In *pancreatic β cells,* stimulation of α_2 receptors reduces the formation of cAMP → decreased insulin release.

Administration and preparations

CAs are absorbed from the intestine but are rapidly degraded by MAO and COMT present in the intestinal wall and liver. They are thus orally inactive.

1. *Adrenaline (Epinephrine)* For systemic action, 0.2–0.5 mg s.c., i.m., action lasts ½ to 2 hrs. ADRENALINE 1 mg/ml inj; ADRENA 4 mg (of Adr. bitartrate=2mg Adr. base)/2 ml inj.

As local vasoconstrictor, 1 in 200,000 to 1 in 100,000 added to lidocaine;

in XYLOCAINE with ADRENALINE: lidocaine 21.3 mg + adrenaline 0.005 mg/ml inj; 30 ml vial.

2. *Noradrenaline (Norepinephrine, levarterenol)* 2–4 µg/min i.v. infusion; local tissue necrosis occurs if the solution extravasates; do not mix with $NaHCO_3$ in the same bottle (rapid oxidation occurs); action starts declining within 5 min of discontinuing infusion. It is rarely used now as a pressor agent. ADRENOR, NORAD, VASCUE, NORDRIN 2 mg (base)/2 ml amp.

3. *Isoprenaline (Isoproterenol)* 20 mg sublingual, 1–2 mg i.m., 5–10 µg/min i.v. infusion; action lasts 1–3 hrs. It is occasionally used to maintain idioventricular rate till pacemaker is implanted. For bronchial asthma, it has been superseded by selective β_2 agonists. ISOPRIN, ISOSOL 4 mg/2 ml inj, NEOEPININE 20 mg sublingual tablets.

Adverse effects and contraindications

- Transient restlessness, headache, palpitation, anxiety, tremor and pallor may occur after s.c./i.m. injection of Adr.
- Marked rise in BP leading to cerebral haemorrhage, ventricular tachycardia/fibrillation, angina, myocardial infarction are the hazards of large doses or inadvertant i.v. injection of Adr.
- Adr is contraindicated in hypertensive, hyperthyroid and angina patients.
- Adr should not be given during anaesthesia with halothane (risk of arrhythmias) and to patients receiving β blockers (marked rise in BP can occur due to unopposed α action).

THERAPEUTIC CLASSIFICATION OF ADRENERGIC DRUGS

I. *Pressor agents*

Noradrenaline	Phenylephrine
Ephedrine	Methoxamine
Dopamine	Mephentermine

II. *Cardiac stimulants*

Adrenaline	Dobutamine
Isoprenaline	

III. *Bronchodilators*

Isoprenaline	Salmeterol
Salbutamol	Formoterol
(Albuterol)	Bambuterol
Terbutaline	

IV. *Nasal decongestants*

Phenylephrine	Naphazoline
Xylometazoline	Pseudoephedrine
Oxymetazoline	Phenyl propanolamine

V. *CNS stimulants*

Amphetamine	Methamphetamine
Dexamphetamine	

VI. *Anorectics*

Fenfluramine	Sibutramine
Dexfenfluramine	

VII. *Uterine relaxant and vasodilators*

Ritodrine	Salbutamol
Isoxsuprine	Terbutaline

Salient features of important adrenergic drugs are described below.

Dopamine (DA)   It is a dopaminergic (D1 and D2) as well as adrenergic α and β_1 (but not β_2) agonist. The D1 receptors in renal and mesenteric blood vessels are the most sensitive: i.v. infusion of low dose of DA dilates these vessels (by raising intracellular cAMP). This increases g.f.r. In addition DA exerts natriuretic effect by D1 receptors on proximal tubular cells. Moderately high doses produce a positive inotropic (direct β_1 and D1 action + that due to NA release), but little chronotropic effect on heart. Vasoconstriction (α_1 action) occurs only when large doses are infused. At doses normally employed, it raises cardiac output and systolic BP with little effect on diastolic BP. It has practically no effect on nonvascular α and β receptors; does not penetrate blood-brain barrier—no CNS effects.

Dopamine is used in patients of cardiogenic or septic shock and severe CHF wherein it increases BP and urine outflow. It is administered by i.v. infusion (0.2–1 mg/min) which is regulated by monitoring BP and rate of urine formation.
DOPAMINE, INTROPIN, DOPACARD 200 mg in 5 ml amp.

Dobutamine   A derivative of DA, but not a D1 or D2 receptor agonist. Though it acts on both α and β adrenergic receptors, the only prominent action of clinically employed doses (2–8 μg/kg/min i.v. infusion) is increased force of cardiac contraction and output, without significant change in heart rate, peripheral resistance and BP. As such, it is considered to be a relatively selective β_1 agonist. It is used as an inotropic agent in pump failure accompanying myocardial infarction, cardiac surgery, and for short term management of severe congestive heart failure. It is less arrhythmogenic than Adr.
CRDIJECT 50 mg/4 ml and 250 mg per 20 ml amp, DOBUTREX, DOBUSTAT 250 mg vial.

Ephedrine   It is an alkaloid obtained from *Ephedra vulgaris*. Mainly acts indirectly but has some direct action as well on α and β receptors. Repeated injections produce tachyphylaxis, primarily because the neuronal pool of NA available for displacement is small. It is resistant to MAO, therefore, effective orally. It is about 100 times less potent than Adr, but longer acting (4–6 hours). Ephedrine crosses to brain and causes stimulation, but central: peripheral activity ratio is lower than that of amphetamine.

Ephedrine can be used for a variety of purposes, but it lacks selectivity, and efficacy is low. Use is now restricted to that in mild chronic bronchial asthma and for hypotension during spinal anaesthesia; occasionally for postural hypotension; 15–60 mg TDS.
EPHEDRINE HCl 15, 30 mg tab; SULFIDRIN 50 mg in 1 ml inj, in ENDRINE 0.75% nasal drops.

Amphetamines   These are synthetic compounds having a pharmacological profile similar to ephedrine; orally active with relatively long duration (4–6 hours). They exert potent CNS stimulant and weaker peripheral cardiovascular actions. Maximal selectivity is exhibited by dextroamphetamine and methamphetamine, which in the usual doses produce few peripheral effects.

The central actions of amphetamines are largely mediated by release of NA from adrenergic neurones in the brain. This occurs mainly by *exchange diffusion* and *reverse transport* involving transporters like NET, DAT and VMAT2 as depicted in Fig. 9.5. However, the effects on locomotor activity, perception and the psychotic phenomena seen at high doses are probably due
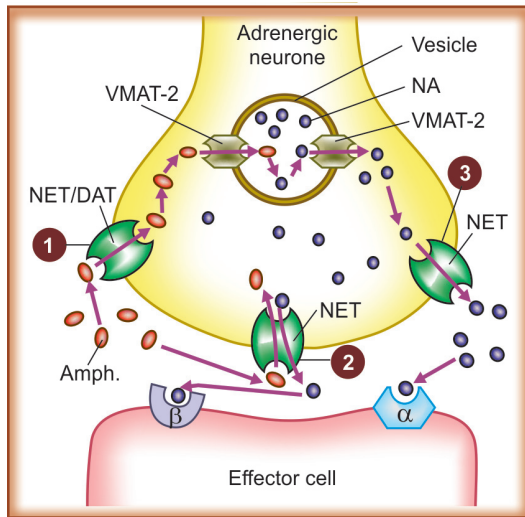
Fig. 9.5: Illustration of the mechanisms of noradrenaline release by amphetamine. Amphetamine (Amph) enters the adrenergic neurone by utilizing the neuronal norepinephrine transporter (NET) or dopamine transporter (DAT)-(1), and then the storage vesicles through vesicular monoamine transporter (VMAT2). It then displaces the stored noradrenaline (NA) into the neuronal cytoplasm, most of which is released into the synaptic cleft by exchange diffusion-(2) with extracellular Amph., or by reverse transport-(3), both utilizing NET. Note that this release is not exocytotic and does not require Ca^{2+}.

to DA and 5-HT release by processes similar to that for NA release. In addition, amphetamine inhibits neuronal reuptake of DA.

The central effects include alertness, increased concentration and attention span, euphoria, talkativeness, increased work capacity. Fatigue is allayed. Athletic performance is improved temporarily followed by deterioration. It is one of the drugs included in the 'dope test' for athletes. The reticular activating system is stimulated resulting in wakefulness and postponement of sleep deprivation induced physical disability. But this is short-lived and may be accompanied by anxiety, restlessness, tremor, dysphoria and agitation. Use before examinations to keep awake can be counter productive and needs to be condemned.

Amphetamines stimulate respiratory centre, specially if it has been depressed. Hunger is suppressed as a result of inhibition of hypo-

thalamic feeding centre. They also have weak anticonvulsant, analgesic and antiemetic actions: potentiate antiepileptics, analgesics and antimotion-sickness drugs. Peripheral effects on heart and BP are not significant at the usual doses (which cause only slight rise in BP), but tone of vesical sphincter is definitely increased.

Amphetamines are drugs of abuse and are capable of producing marked psychological but little or no physical dependence. Amphetamine abusers are generally teenagers seeking thrill or kick which is obtained on rapid i.v. injection. High doses produce euphoria, restlessness, insomnia, aggression, panic, marked excitement which may progress to mental confusion, delirium, hallucinations and an acute psychotic state. Peripheral component of toxicity includes rise in BP, palpitation, arrhythmias, vomiting, abdominal cramps and vascular collapse. Death is usually preceded by convulsions and coma.

Repeated use is more likely to produce long lasting behavioural abnormalities; psychosis may be precipitated.

Tolerance to central actions and toxic effects of amphetamine develops, and is both pharmacokinetic as well as pharmacodynamic. Starvation due to suppression of appetite produces acidic urine; amphetamine is ionized more at acidic pH and is excreted more rapidly.

Treatment of amphetamine toxicity includes administration of chlorpromazine which controls both central as well as peripheral α adrenergic effects.

Amphetamine: 5–15 mg oral; Dexamphetamine: 5–10 mg (children 2.5–5 mg) oral.
Methamphetamine: 5–10 mg oral.

Phenylephrine   It is a selective α_1 agonist, has negligible β action. It raises BP by causing vasoconstriction. Because it has little cardiac action, reflex bradycardia is prominent. Topically it is used as a nasal decongestant and in the eye for producing mydriasis when cycloplegia is not required. Phenylephrine tends to reduce intraocular tension by constricting ciliary body blood vessels. It is also a frequent constituent of orally administered nasal decongestant preparations.

Central effects are not seen with usual clinical doses.

Dose: 2–5 mg i.m., 0.1–0.5 mg slow i.v. inj, 30–60 µg/min i.v. infusion; 5–10 mg oral; 0.25–0.5% nasal instillation; 5–10% topically in eye;

FRENIN 10 mg in 1 ml inj; DECOLD PLUS 5 mg with paracetamol 400 mg + chlorpheniramine 2 mg + caffeine 15 mg tab., SINAREST 10 mg with chlorpheniramine 2 mg, paracetamol 500 mg, caffeine 30 mg tab, FENOX 0.25% with nephazoline 0.025% nasal drops, DROSYN 10% eye drops, in DROSYN-T, TROPAC-P 5% with tropicamide 0.8% eye drops.

Methoxamine   Another selective α_1 agonist with no β actions (has weak β blocking action). Resembles phenylephrine very closely. Occasionally used as a pressor agent.

Dose: 10–20 mg i.m.; 3–5 mg slow i.v. inj.

VASOXINE 20 mg/ml inj.

Mephentermine   It produces both cardiac stimulation and vasoconstriction by directly activating α and β adrenergic receptors as well as by releasing NA. Cardiac output, systolic and diastolic BP are increased. The direct positive chronotropic effect on heart is generally counter balanced by vagal stimulation due to rise in mean BP.

Mephentermine is not a substrate for either MAO or COMT. Therefore it is active orally with longer duration of action (2–6 hr). It crosses blood-brain barrier to some extent—may produce excitatory effects at higher doses. It is used to prevent and treat hypotension due to spinal anaesthesia and surgical procedures, shock in myocardial infarction and other hypotensive states.

Dose: 10–20 mg oral/i.m., also by slow i.v. infusion.

MEPHENTINE 10 mg tab, 15 mg in 1 ml amp, 30 mg/ml in 10 ml vial.

SELECTIVE β_2 STIMULANTS

These include, salbutamol, terbutaline, salmeterol, formoterol and ritodrine. They cause bronchodilatation, vasodilatation and uterine relaxation, without producing significant cardiac stimulation. β_2 selectivity is only relative. Salbutamol has $\beta_2:\beta_1$ action ratio of about 10. They are primarily used in bronchial asthma (for description *see* Ch. 16). Other uses are:

• As uterine relaxant to delay premature labour. Ritodrine is the preferred drug (*see* Ch. 23);
• In hyperkalaemic familial periodic paralysis— β_2 agonists benefit by enhancing K^+ uptake into muscles, thereby lowering plasma K^+ levels.

The most important side effect is muscle tremor; tachycardia and arrhythmias are less likely.

Isoxsuprine   It is an orally effective long-acting β receptor stimulant which has direct smooth muscle relaxant property as well. It has been used as uterine relaxant for threatened abortion and dysmenorrhoea, but efficacy is poor. Beneficial effects in peripheral and cerebral vascular diseases are disappointing.

Side effects: nausea, tachycardia, flushing, hypotension, dizziness, tremor.

Dose: 5–10 mg oral, i.m. 4–6 hourly,

DUVADILAN 10 mg tab, 40 mg SR cap, 10 mg/2 ml inj.

NASAL DECONGESTANTS

These are α agonists which on topical application as dilute solution (0.05–0.1%) produce local vasoconstriction. The imidazoline compounds—naphazoline, xylometazoline and oxymetazoline are relatively selective α_2 agonist (like clonidine). They have a longer duration of action (12 hours) than ephedrine. After-congestion is claimed to be less than that with ephedrine or phenylephrine. They may cause initial stinging sensation (specially naphazoline). Regular use of these agents for long periods should be avoided because mucosal ciliary function is impaired: atrophic rhinitis and anosmia can occur due to persistent vasoconstriction. They can be absorbed from the nose and produce systemic effects, mainly CNS depression and rise in BP. These drugs should be used cautiously in hypertensives and in those receiving MAO inhibitors.

Xylometazoline: 0.05–0.1% topical in nose; OTRIVIN 0.05% (pediatric), 0.1% (adult) nasal drops and nasal spray.

Oxymetazoline: 0.025–0.05% topical in nose; NASIVION, SINAREST 0.025% (pediatric), 0.05% nasal drops.

Naphazoline: 0.1% topical in nose; PRIVINE 0.1% nasal drops.

Pseudophedrine   A stereoisomer of ephedrine; causes vasoconstriction, especially in mucosae and

skin, but has fewer CNS and cardiac effect and is a poor bronchodilator (little β_2 agonistic activity). It has been used orally as a decongestant of upper respiratory tract, nose and eustachian tubes. Combined with antihistaminics, mucolytics, antitussives and analgesics, it is believed to afford symptomatic relief in common cold, allergic rhinitis, blocked eustachian tubes and upper respiratory tract infections. However, no selective action on these vascular beds has been demonstrated; rise in BP can occur, especially in hypertensives.

Dose: 30–60 mg TDS.

SUDAFED 60 mg tab, 30 mg/5 ml syrup; in SINAREST 60 mg with chlorpheniramine 2 mg + caffeine 30 mg + paracetamol 500 mg tab; in CHESTON 30 mg with chlorpheniramine 2 mg + bromhexine 4 mg per tab/5 ml syr; in ACTICOLD 60 mg with chlorpheniramine 4 mg + paracetamol 500 mg tab; in CODYLEX 60 mg with chlorpheniramine 4 mg + ibuprofen 400 mg tab.

Phenylpropanolamine (PPA) Being chemically and pharmacologically similar to ephedrine, PPA causes vasoconstriction and has some amphetamine like CNS effects, including suppression of hunger. It was included in a large number of oral cold/decongestant combination remedies, and in USA it was used as an appetite suppressant as well.

Following reports and case control studies associating PPA use with haemorrhagic stroke and concerns regarding its potential to precipitate behavioural/psychiatric disturbances, many countries, led by USA, prohibited the sale of PPA containing medicines decades back. However, oral decongestant formulations containing relatively lower amounts of PPA (25–50 mg) continued to be available over-the-counter in India till recently. All such preparations have now been banned since March 2011[*].

ANORECTIC AGENTS

Though amphetamines suppress appetite, their use as anorectic agents is precluded by thier adverse central effects. A number of related drugs have been developed which inhibit feeding centre (like amphetamine) but have little/no CNS stimulant action or abuse liability. All of them act by releasing (reverse transport) or by inhibiting the reuptake of NA/DA or 5-HT, enhancing monoaminergic transmission in the brain. Accordingly they may be grouped into:

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* The ban order is presently under court stay.

Noradrenergic agents: Phentermine, phenylpropanolamine (PPA), diethylpropion, mazindol.

Serotonergic agents: Fenfluramine, dexfenfluramine.

Noradrenergic/serotonergic agent: Sibutramine.

The noradrenergic agents activate hypothalamic adrenergic/dopaminergic receptors, have residual stimulatory effects; interfere with sleep and primarily affect the appetite centre. On the other hand, serotonergic agents have mild sedating property and primarily affect the satiety centre.

Fenfluramine and *dexfenfluramine* reduce food seeking behaviour by enhancing serotonergic transmission in the hypothalamus.

They were extensively used by slimming centres, though tolerance to the anorectic action develops in 2-3 months. In the late 1990s ecocardiographic abnormalities, valvular defects, pulmonary hypertension and sudden deaths were related to the use of a combined preparation of fenfluramine + phentermine. The US-FDA recommended discontinuation of fenfluramine, dexfenfluramine and their combinations. Most other countries, including India followed.

Sibutramine and R-Sibutramine Introduced subsequently, these drugs inhibit both NA and 5-HT reuptake in the hypothalamus, suppress appetite in a manner similar to fenfluramine, and probably increase thermogenesis by activating adrenergic β_3 mechanism in adipose tissue. These drugs caused weight loss in obese people and were routinely used by slimming centres. Several side effects were noted; serious adverse reactions, including cardiovascular events and death were reported to the US-FDA and drug committees in Europe leading to ban on their use. After its own assessment, India has also banned these drugs from March 2011.

THERAPEUTIC USES

1. Vascular uses

(i) *Hypotensive states* (shock, spinal anaesthesia, hypotensive drugs) One of the pressor agents can be used along with volume replacement for neurogenic and haemorrhagic shock; also as an expedient measure to maintain cerebral circulation for other varieties of shock. They should not be used in secondary shock when reflex vasoconstriction is already marked. Use in cardiogenic shock is tricky, because attempts to raise BP may also increase cardiac work. Slow i.v. infusion of dopamine/dobutamine is more appropriate in this situation. Dopamine increases cardiac contactility without causing significant tachycardia. It also

improves renal blood flow and may help to raise B.P. Dobutamine has relatively more selective inotropic effect. Use of NA is practically obsolete. Adr 0.5 mg injected promptly i.m. is the drug of choice in anaphylactic shock (*see* p. 87). It not only raises BP, but counteracts bronchospasm/ laryngeal edema that may accompany. Because of the rapidity and profile of action Adr is the only life saving measure. Oral ephedrine has been used to treat postural hypotension due to autonomic neuropathy, which may be age related, idiopathic or secondary to diabetes, etc. However, no pressor agent is entirely satisfactory because it cannot mimic selective NA release that occurs only on standing. Elastic stockings and use of fludrocortisone to expand plasma volume are more helpful.

(ii) *Along with local anaesthetics*   Adr 1 in 200,000 to 1 in 100,000 for infiltration, nerve block and spinal anaesthesia. Duration of anaesthesia is prolonged and systemic toxicity of local anaesthetic is reduced. Local bleeding is minimised (*see* Ch. 26).

(iii) *Control of local bleeding*   From skin and mucous membranes, e.g. epistaxis : compresses of Adr 1 in 10,000, phenylephrine/ephedrine 1% soaked in cotton can control arteriolar and capillary bleeding. NA 8 mg in 100–200 ml saline put in stomach through a tube can control bleeding from gastric erosions and stress ulcers.

(iv) *Nasal decongestant*   In colds, rhinitis, sinusitis, blocked nose or eustachian tube—one of the α-agonists is used as nasal drops. Shrinkage of mucosa provides relief, but after-congestion, atrophy of mucosa on prolonged use are still a problem. The imidazolines should be used in lower concentrations in infants and young children, because they are more sensitive to central effects of these drugs. Nasal decongestants should be used very cautiously in hypertensive patients and in elderly males.

    Pseudoephedrine and phenylephrine have been used orally as decongestants, but effective doses will constrict other blood vessels as well and cause rise in BP. However, oral vasoconstrictors do not produce after-congestion.

(v) *Peripheral vascular diseases*   like Buerger's disease, Raynaud's phenomena, diabetic vascular insufficiency, gangrene, frost bite, ischaemic ulcers, night leg cramps, cerebral vascular inadequacy : vasodilators including isoxsuprine have been used, but are far from satisfactory in most cases, because often the capacity of the affected vessels to dilate is severely limited, and ischaemia itself is a potent vasodilator.

2. Cardiac uses

(i) *Cardiac arrest* (drowning, electrocution, Stokes-Adams syndrome and other causes) Adr may be used to stimulate the heart; i.v. adminis- tration is justified in this setting with external cardiac massage.

(ii) *Partial or complete A-V block*   Isoprenaline may be used as temporary measure to maintain sufficient ventricular rate.

(iii) *Congestive heart failure (CHF)* Adrenergic inotropic drugs are not useful in the routine treatment of CHF. However, controlled short term i.v. infusion of DA/dobutamine can tide over acute cardiac decompensation during myocardial infarction, cardiac surgery and in resistant CHF.

3. Bronchial asthma and COPD Adrenergic drugs, especially β_2 stimulants are the primary drugs forrelief of reversible airway obstruction (*see* Ch. 16).

4. Allergic disorders   Adr is a physiological antagonist of histamine which is an important mediator of many acute hypersensitivity reactions. It affords quick relief in urticaria, angioedema; is life saving in laryngeal edema and anaphylaxis. It is ineffective in delayed, retarded and other types of allergies, because histamine is not involved.

5. Mydriatic   Phenylephrine is used to facili- tate fundus examination; cycloplegia is not required. It tends to reduce intraocular tension in wide angle glaucoma. The ester prodrug of Adr dipivefrine is an adjuvant drug for open angle glaucoma (*see* p. 154).

6. Central uses

(i) *Attention deficit hyperkinetic disorder (ADHD):* also called minimal brain dysfunction, is usually detected in childhood and the sufferer is considered a 'hyperkinetic child', (*see* Ch. 35 also). Amphetamines have an apparently paradoxical effect to calm down hyperkinetic children. This disorder is recognized as a mild grade of mental retardation or a reduction in the ability to concentrate, i.e. the span of time for which attention can be focused on a subject is abbreviated. Amphetamines by increasing attention span improve behaviour and performance in studies; tolerance to this effect does not develop. However, growth retardation may occur due to reduction in appetite. The risk-benefit ratio of such therapy often disfavours use of amphetamine.

(ii) *Narcolepsy* Narcolepsy is sleep occurring in fits and is adequately controlled by amphetamines. Development of tolerance, abuse and behavioural abnormalities are the calculated risks of such therapy. Modafinil, a newer psychostimulant with less dependence inducing potential, is being preferred now (*see* Ch. 35). Imipramine-like drugs are also useful in some patients, and are safer.

(iii) *Epilepsy* Amphetamines are occasionally used as adjuvants and to counteract sedation caused by antiepileptics.

(iv) *Parkinsonism* Amphetamines improve mood and reduce rigidity (slightly) but do not benefit tremor. They are occasionally used as adjuvants in parkinsonism.

(v) *Obesity* The anorectic drugs can help the obese to tolerate a reducing diet for short periods, but do not improve the long-term outlook. Their use may be considered in severe obesity, but not for cosmetic reasons or for figure improvement. In the absence of dietary restriction none of them has any significant weight reducing effect, and lifestyle modification is required. Currently there is no approved sympathomimetic anorectic drug.

The newer approaches being developed for control of obesity are:

Orlistat An inhibitor of gastric and pancreatic lipase; it interferes with digestion and absorption of dietary triglycerides. Absorption of cholesterol and fat soluble vitamins is also impaired. It has facilitated weight loss in clinical trials. Fluid motions, steatorrhoea, abdominal pain, nausea, flatulence and vitamin deficiency are the side effects.
Dose: 120 mg with meals 3 times a day.
OBELIT, ORIDUCE, ZEROFAT 120 mg tab.

Olestra is a sucrose polyester which can be used as a cooking medium in place of fat but is neither digested nor absorbed. Its acceptability is inconsistent.

Leptin (the endogenous slimming peptide) *analogues, neuropeptide Y antagonists and β₃ adrenergic agonists* are under investigation as antiobesity drugs.

Rimonabant This selective cannabinoid (CB-1) receptor antagonist was used briefly as appetite reducing drug, but soon serious adverse reaction reports appeared and it was banned in Europe and USA. India followed suit in Dec. 2009.

7. Nocturnal enuresis in children and urinary incontinence
Amphetamine affords benefit both by its central action as well as by increasing tone of vesical sphincter.

8. Uterine relaxant
Isoxsuprine has been used in threatened abortion and dysmenorrhoea, but efficacy is doubtful. Selective β_2 stimulants, especially ritodrine, infused i.v. has been successfully used to postpone labour but maternal morbidity and mortality may be increased due to its cardiac and metabolic actions and incidents of pulmonary edema (*see* Ch. 23).

9. Insulin hypoglycaemia
Adr may be used as an expedient measure, but glucose should be given as soon as possible.

☞ PROBLEM DIRECTED STUDY

9.1 A lady aged 55 years presented for eye checkup. She has been having visual difficulty over the past few months, and lately she had started noticing 'halos' around the lights. She also has dull chronic ache in the forehead region. Tonometry revealed her intraocular pressure (i.o.p.) to be 22 and 24 mm Hg respectively in the left and right eye.
(a) Which mydriatic will be suitable for dilating her pupil for fundus examination and why?
(see Appendix-1 for solution)

CHAPTER 9

Chapter 10 Antiadrenergic Drugs (Adrenergic Receptor Antagonists) and Drugs for Glaucoma

These are drugs which antagonize the receptor action of adrenaline and related drugs. They are competitive antagonists at α or β or both α and β adrenergic receptors and differ in important ways from the "adrenergic neurone blocking agents", which act by interfering with the release of adrenergic transmitter on nerve stimulation. These differences are given in Table 10.1.

α ADRENERGIC BLOCKING DRUGS

These drugs inhibit adrenergic responses mediated through the α adrenergic receptors without affecting those mediated through β receptors.

CLASSIFICATION

I. *Nonequilibrium type*
   (i) β-*Haloalkylamines*—Phenoxybenzamine.

II. *Equilibrium type (competitive)*

A. Nonselective
  (i) *Ergot alkaloids*—Ergotamine, Ergotoxine
  (ii) *Hydrogenated ergot alkaloids*—Dihydro-ergotamine (DHE), Dihydroergotoxine
  (iii) *Imidazoline*—Phentolamine
  (iv) *Miscellaneous*–Chlorpromazine

B. α_1 selective—Prazosin, Terazosin, Doxazosin, Alfuzosin, Tamsulosin

C. α_2 selective—Yohimbine

GENERAL EFFECTS OF α BLOCKERS

1. Blockade of vasoconstrictor α_1 (also α_2) receptors reduces peripheral resistance and causes pooling of blood in capacitance vessels → venous return and cardiac output are reduced → fall in BP. Postural reflex is interfered with → marked *hypotension* occurs on standing → dizziness and syncope. Hypovolemia accentuates the hypotension. The α blockers abolish the pressor action of Adr (injected i.v. in animals), which then produces only fall in BP due to β_2 mediated vasodilatation. This was first demonstrated by Sir HH Dale (1913) and is called *vasomotor reversal of Dale*. Pressor and other actions of selective α agonists (phenylephrine) are suppressed.

2. Reflex *tachycardia* occurs due to fall in mean arterial pressure and increased release of NA due to blockade of presynaptic α_2 receptors.

3. *Nasal stuffiness* and *miosis* result from blockade of α receptors in nasal blood vessels and in radial muscles of iris respectively.

4. Intestinal motility is increased due to partial inhibition of relaxant sympathetic influences—loose motion may occur.

5. Hypotension produced by α blockers can reduce renal blood flow → g.f.r. is reduced and more complete reabsorption of Na^+ and water occurs in the tubules → Na^+ *retention* and *expansion of blood volume*. This is accentuated by reflex increase in renin release mediated through β_1 receptors.

6. Tone of smooth muscle in bladder trigone, sphincter and prostate is reduced by blockade of α_1 receptors (mostly of the α_{1A} subtype) → *urine flow in patients with* benign hypertrophy of prostate *(BHP) is improved*.

7. Contractions of vas deferens and related organs which result in ejaculation are coordinated through α receptors—α blockers can *inhibit ejaculation*; this may manifest as *impotence*.

The α blockers have no effect on adrenergic cardiac stimulation, bronchodilatation, vasodilatation and most of the metabolic changes, because these are mediated predominantly through β receptors.

TABLE 10.1	Differences between antiadrenergic and adrenergic neurone blocking drugs	
	Antiadrenergic drugs	*Adrenergic neurone blocking drugs*
1. Locus of action	Adrenergic receptors on effector cells or neurones	Adrenergic neuronal membrane or contents
2. Effects of adrenergic nerve stimulation	Blocked (less completely)	Blocked (more completely)
3. Effect of injected Adr	Blocked	Not blocked (may be potentiated)
4. Type of effects blocked by a single drug	Either α or β (except Labetalol and its congeners)	Sympathetic function decreased irrespective of the receptor type
5. Examples	α—Phentolamine β—Propranolol	Reserpine, Guanethidine, Bretylium, α-methyl-p-tyrosine

Apart from these common effects, most of which manifest as side effects, many α blockers have some additional actions. The pharmacological profile of an α blocker is mainly governed by its central effects and by the relative activity on α_1 and α_2 receptor subtypes. Only the distinctive features of individual α blockers are described below.

Phenoxybenzamine It cyclizes spontaneously in the body giving rise to a highly reactive ethyleniminium intermediate which reacts with α adrenoceptors and other biomolecules by forming strong covalent bonds. The α blockade is of nonequilibrium (irreversible) type and develops gradually (even after i.v. injection) and lasts for 3–4 days till fresh receptors are synthesized.

Partial blockade of 5-HT, histaminergic and cholinergic receptors, but not β adrenergic receptors, can be demonstrated at higher doses.

The fall in BP caused by phenoxybenzamine is mainly postural because venodilatation is more prominent than arteriolar dilatation. In recumbent subjects cardiac output and blood flow to many organs is increased due to reduction in peripheral resistance and increased venous return. It tends to shift blood from pulmonary to systemic circuit because of differential action on the two vascular beds. It also tends to shift fluid from extravascular to vascular compartment. Phenoxybenzamine is lipid soluble, penetrates brain and can produce CNS stimulation, nausea and vomiting on rapid i.v. injection. However, oral doses produce depression, tiredness and lethargy. Major side effects are postural hypotension, palpitation, nasal blockage, miosis, inhibition of ejaculation.

Pharmacokinetics Oral absorption of phenoxybenzamine is erratic and incomplete; i.m. and s.c. injections are very painful—should not be given. Though most of the administered dose is excreted in urine in 24 hours, small amounts that have covalently reacted remain in tissues for long periods. Chronic administration leads to accumulation in adipose tissue.
Dose: 20–60 mg/day oral; 1 mg/kg by slow i.v. infusion over 1 hour; used primarily in pheochromocytoma, occasionally in secondary shock and peripheral vascular disease. FENOXENE 10 mg cap, 50 mg/ml inj. BIOPHENOX 50 mg in 1 ml inj.

Natural and hydrogenated ergot alkaloids (*see* Ch. 12 and Ch. 21) Ergot alkaloids are the adrenergic antagonists with which Dale demonstrated the vasomotor reversal phenomenon. The amino acid alkaloids *ergotamine* and *ergotoxine* are partial agonists and antagonists at α adrenergic, serotonergic and dopaminergic receptors. The amine alkaloid *ergometrine* has no α blocking activity.

The natural ergot alkaloids produce long lasting vasoconstriction which predominates over their α blocking action—peripheral vascular insufficiency and gangrene of toes and fingers occurs in ergotism. Ergotoxine is a more potent α blocker and less potent vasoconstrictor than ergotamine. Hydrogenation reduces vasoconstrictor and increases α blocking activity.

The α blockade produced by ergot alkaloids is low grade and clinically not useful. Their principal use is in migraine (*see* Ch. 12). Dihydroergotoxine has been used as a cognition enhancer (*see* Ch. 35).

Phentolamine This is a rapidly acting α blocker with short duration of action (in minutes). It equally blocks α_1 and α_2 receptors—NA release is increased and venodilatation predominates over arteriolar dilatation. It is used as a quick and short acting α blocker for diagnosis and intraoperative

management of pheochromocytoma and for control of hypertension due to clonidine withdrawal, cheese reaction, etc. It is the most suitable α blocker for local infiltration to counteract vasoconstriction due to extravasated NA/DA during their i.v. infusion.
Dose: 5 mg i.v. repeated as required;
REGITINE, FENTANOR 10 mg/ml inj.

Prazosin It is first of the highly selective α_1 blockers having $\alpha_1 : \alpha_2$ selectivity ratio 1000:1. All subtypes of α_1 receptor (α_{1A}, α_{1B}, α_{1D}) are blocked equally. It blocks sympathetically mediated vasoconstriction and produces fall in BP which is attended by only mild tachycardia; NA release is not increased due to absence of α_2 blockade.

Prazosin dilates arterioles more than veins. Postural hypotension is less marked, occurs especially in the beginning, which may cause dizziness and fainting as 'first dose effect'. This can be minimized by starting with a low dose and taking it at bedtime. Subsequently tolerance develops to this side effect. Other α blocking side effects (miosis, nasal stuffiness, inhibition of ejaculation) are also milder. For the above reasons, prazosin (also other α_1 blockers) has largely replaced phenoxybenzamine. Prazosin, in addition, inhibits phosphodiesterase which degrades cAMP. Rise in smooth muscle cAMP could contribute to its vasodilator action.

Prazosin is effective orally (bioavailability ~60%), highly bound to plasma proteins (mainly to α_1 acid glycoprotein), metabolized in liver and excreted primarily in bile. Its plasma t½ is 2–3 hours; effect of a single dose lasts for 6–8 hours.

Prazosin is primarily used as an antihypertensive (*see* Ch. 40). Other uses are—Raynaud's disease and benign hypertrophy of prostate (BHP). Prazosin blocks α_1 receptors in bladder trigone and prostatic smooth muscle, thereby improves urine flow, reduces residual urine in bladder.
PRAZOPRES 0.5, 1.0 and 2.0 mg tabs. Start with 0.5–1 mg at bedtime; usual dose 1–4 mg BD or TDS.
MINIPRESS XL: Prazosin GITS (gastrointestinal therapeutic system) 2.5 mg and 5 mg tablets; 1 tab OD.

Terazosin It is chemically and pharmacologically similar to prazosin; differences are higher bioavailability (90%) and longer plasma t½ (~12 hr); a single daily dose lowers BP over 24 hrs. Terazosin is more popular for use in BHP due to single daily dose and a probable apoptosis promoting effect on prostate. This is unrelated to α_1 receptor blockade, but may retard the progression of prostatic hypertrophy.
HYTRIN, TERALFA, OLYSTER 1, 2, 5 mg tab; usual maintenance dose 2–10 mg OD.

Doxazosin Another long acting (t½ 18 hr) congener of prazosin with pharmacological profile, similar to terazosin, including the apoptosis promoting effect on prostate. It is used in hypertension and BHP.
Dose: 1 mg OD initially, increase upto 8 mg BD;
DOXACARD, DURACARD, DOXAPRESS 1, 2, 4 mg tabs.

Alfuzosin This short acting (t½ 3–5 hours) congener of prazosin has been specifically developed for symptomatic treatment of BHP, despite the fact that it is nonselective for α_{1A}, α_{1B} and α_{1D} subtypes. It is not approved as an antihypertensive. The metabolism of alfuzosin is inhibited by CYP34A inhibitors. Concurrent treatment with erythromycin, ketoconazole, ritonavir etc. is to be avoided.
Dose: 2.5 mg BD-QID or 10 mg as extended release (ER) tablet.
ALFUSIN, ALFOO 10 mg ER tab.

Tamsulosin This relatively uroselective α_{1A}/α_{1D} blocker ($\alpha_{1A} : \alpha_{1B}$ affinity 7–38 fold) has been found as effective as terazosin in improving BHP symptoms, because α_{1A} subtype predominate in the bladder base and prostate. However, it lacks the prostatic apoptosis promoting property of terazosin and doxazosin. Tamsulosin does not cause significant changes in BP or HR at doses which relieve urinary symptoms, and it is not used as an antihypertensive. No increase in adverse cardiovascular events has been noted. Postural hypotension is infrequent, dizziness and retrograde ejaculation are the only significant side effects. Problem of floppy iris has been encountered during cataract surgery. Its plasma t½ is 6–9 hrs, but the modified release (MR) cap needs only once daily dosing. It may be a better tolerated α_1 blocker for BHP in patients who continue to suffer postural hypotension with terazosin/doxazosin.

CONTIFLO–OD 0.4 mg Cap, URIMAX, DYNAPRES 0.2, 0.4 mg MR cap; 1 cap (max 2) in the morning with meals. No dose titration is needed in most patients.

Yohimbine An alkaloid from the West African plant *Yohimbehe*. It is a relatively selective α_2 blocker with short duration of action. Also blocks 5-HT receptors. Heart rate and BP are generally elevated due to increased central sympathetic outflow as well as enhanced peripheral NA release. Other CNS effects include excitation, tremor, ADH release (antidiuresis), nausea and vomiting. It may cause congestion in genitals and has been considered to be an aphrodisiac. This effect is only psychological, but can overcome psychogenic impotence in some patients.

There are no valid indications for clinical use of yohimbine.

Chlorpromazine and some other neuroleptics have significant α adrenergic blocking activity—cause fall in BP, nasal stuffiness and inhibition of ejaculation as side effect.

USES OF α BLOCKERS

1. *Pheochromocytoma* It is a tumour of adrenal medullary cells. Excess CAs are secreted which can cause intermittent or persistent hypertension. Estimation of urinary CA metabolites (VMA, normetanephrine) is diagnostic. In addition, pharmacological tests can be performed.

Phentolamine test Inject phentolamine 5 mg i.v. over 1 min in recumbent subject. A fall in BP > 35 mm Hg systolic and/or > 25 mm Hg diastolic is indicative of pheochromocytoma. However, it is not very reliable, both false positive and false negative results are possible.

Provocative tests have been performed by injecting histamine, methacholine or glucagon—which provoke release of CAs and cause marked rise in BP if pheochromocytoma is present. These tests are dangerous; phentolamine must be available to counteract excessive rise in BP.

Therapeutic Phenoxybenzamine can be used as definitive therapy for inoperable and malignant pheochromocytoma. Prazosin is an alternative. When surgical removal of the tumour is contemplated, it is desirable to give phenoxybenzamine orally for 1–2 weeks preoperatively and infuse it i.v. during surgery. The rationale is:
(i) Due to excess circulating CAs blood volume is low (they shift fluid from vascular to extravascular compartment). Treatment with α blocker normalizes blood volume and distribution of body water.

(ii) Handling of the tumour during surgery may cause outpouring of CAs in blood → marked rise in BP. This is prevented by phenoxybenzamine given pre and intraoperatively. Alternatively, phentolamine drip can be instituted during the operation. (iii) Removal of the tumour is often attended by marked fall in BP as blood vessels dilate and the blood volume is low. This does not happen if volume has been restored before hand with the aid of an α blocker.

2. *Hypertension* α blockers other than those selective for α_1 (prazosin-like) have been a failure in the management of essential hypertension, because vasodilatation is compensated by cardiac stimulation. Moreover, postural hypotension, impotence, nasal blockage and other side effects produced by nonselective α blockers are unacceptable. However, phentolamine/phenoxybenzamine are of great value in controlling episodes of rise in BP during clonidine withdrawal and cheese reaction in patients on MAO inhibitors.

3. *Benign hypertrophy of prostate (BHP)* The urinary obstruction caused by BHP has a static component due to increased size of prostate and a dynamic component due to increased tone of bladder neck/prostate smooth muscle. Two classes of drugs are available:
- α_1 adrenergic blockers (prazosin like): decrease tone of prostatic/bladder neck muscles.
- 5-α reductase inhibitor (finasteride): arrest growth/reduce size of prostate (*see* Ch. 21).
Since activation of α_1 adrenoceptors in bladder trigone, prostate and prostatic urethra increases smooth muscle tone, their blockade relaxes these structures, reducing dynamic obstruction, increasing urinary flow rate and causing more complete emptying of bladder in many patients of BHP.

Voiding symptoms (hesitancy, narrowing of stream, dribbling and increased residual urine) are relieved better than irritative symptoms like urgency, frequency and nocturia. The α_1 blockers afford faster (within 2 weeks) and greater symptomatic relief than finasteride which primarily affects static component of obstruction and has a delayed onset taking nearly six months for clinical improvement. The α_1 blockers do not affect prostate size, but are more commonly used.

However, effects last only till the drug is given. Even with continued therapy, benefit may decline after few years due to disease progression. They may be used concurrently with finasteride.

Terazosin, doxazosin, alfuzosin and tamsulosin are the peferred α_1 blockers because of once daily dosing. There is some evidence that terazosin and doxazosin promote apoptosis in prostate. Tamsulosin appears to cause fewer vascular side effects because of relative α_{1A}/α_{1D} selectivity.

4. *Secondary shock* Shock due to blood or fluid loss is accompanied by reflex vasoconstriction. If volume replacement fails to reverse this (extremities remain pale and cold, pulse pressure does not improve), therapy with an α blocker (phenoxybenzamine i.v.) can help by:
(i) Counteracting vasoconstriction.
(ii) Shifting blood from pulmonary to systemic circuit.
(iii) Returning fluid from extravascular to the vascular compartment so that cardiac output improves.

5. *Peripheral vascular diseases* α blockers do increase skin and to some extent muscle blood flow in normal individuals, but these drugs are largely disappointing in peripheral vascular diseases when obstruction is organic (Buerger's disease). However, when vasoconstriction is a prominent feature (Raynaud's phenomenon, acrocyanosis), good symptomatic relief is afforded by prazosin or phenoxybenzamine.

6. *Congestive heart failure (CHF)* The vasodilator action of prazosin can afford symptomatic relief in selected patients of CHF in the short-term, but long-term prognosis is not improved.

7. *Papaverine/Phentolamine Induced Penile Erection (PIPE) therapy for impotence* In patients unable to achieve erection, injection of papaverine (3–20 mg) with or without phentolamine (0.5–1 mg) in the corpus cavernosum has been found to produce penile tumescence to permit intercourse. However, the procedure requires skill and training. Priapism occurs in 2–15% cases, which if not promptly treated leads to permanent damage. This is reversed by aspirating blood from the corpus cavernosum or by injecting phenylephrine locally. Repeated injections can cause penile fibrosis. Other complications are—local haematoma, infection, paresthesia and penile deviation. This therapy should therefore be reserved for selected situations with proper facilities.

β ADRENERGIC BLOCKING DRUGS

These drugs inhibit adrenergic responses mediated through the β receptors.

The dichloro derivative of isoprenaline was the first compound found in 1958 to block adrenergic responses which could not be blocked till then by the available adrenergic antagonists. However, it was not suitable for clinical use. *Propranolol* introduced in 1963 was a therapeutic breakthrough. Since then, drugs in this class have proliferated and diversified.

All β blockers are competitive antagonists. Propranolol blocks β_1 and β_2 receptors, but has weak activity on β_3 subtype. It is also an inverse agonist: reduces resting heart rate as well. Some β blockers like metoprolol, atenolol, etc. preferentially block β_1 receptors, while few others have additional α_1 receptor blocking and/or vasodilator properties.

CLASSIFICATION

Nonselective (β_1 and β_2)
a. *Without intrinsic sympathomimetic activity*
   Propranolol, Sotalol, Timolol.
b. *With intrinsic sympathomimetic activity*
   Pindolol
c. *With additional α blocking property*
   Labetalol, Carvedilol

Cardioselective (β_1)
   Metoprolol, Atenolol, Acebutolol, Bisoprolol, Esmolol, Betaxolol, Celiprolol, Nebivolol
The pharmacology of propranolol is described as prototype.

PROPRANOLOL

Another system classifies β blockers into 3 generations.

First generation (older, nonselective)	Second generation (β_1 selective)	Third generation (with additional α blocking and/or vasodilator property)
Propranolol	Metoprolol	Labetalol
Timolol	Atenolol	Carvedilol
Sotalol	Acebutolol	Celiprolol
Pindolol	Bisoprolol	Nebivolol
	Esmolol	Betaxolol
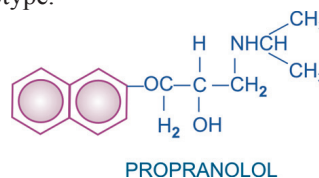
PHARMACOLOGICAL ACTIONS

1. CVS

(a) Heart Propranolol decreases heart rate, force of contraction (at relatively higher doses) and cardiac output (c.o.). It prolongs systole by retarding conduction so that synergy of contraction of ventricular fibres is disturbed. The effects on a normal resting subject are mild, but become prominent under sympathetic overactivity (exercise, emotion). Ventricular dimensions are decreased in normal subjects, but dilatation can occur in those with reduced reserve—CHF may be precipitated or aggravated.

Cardiac work and oxygen consumption are reduced as the product of heart rate and aortic pressure decreases. Total coronary flow is reduced (blockade of dilator β receptors), but this is largely restricted to the subepicardial region, while perfusion of the subendocardial area (which is the site of ischaemia in angina patients) is not affected. The overall effect in angina patients is improvement of O_2 supply/demand status; exercise tolerance is increased.

Propranolol abbreviates refractory period of myocardial fibres and decreases automaticity— rate of diastolic depolarization in ectopic foci is reduced, specially if it had been augmented by adrenergic stimuli. The A-V conduction is delayed. At high doses a direct depressant and membrane stabilizing (quinidine like) action is exerted, but this contributes little to the antiarrhythmic effect at usual doses. Propranolol blocks cardiac stimulant action of adrenergic drugs but not that of digoxin, methylxanthines or glucagon.

(b) Blood vessels Propranolol blocks vaso-dilatation and fall in BP evoked by isoprenaline and enhances the rise in BP caused by Adr. There is re-reversal of vasomotor reversal that is seen after a blockade. Propranolol has no direct effect on blood vessels and there is little acute change in BP. On prolonged administration BP gradually falls in hypertensive subjects but not in normo-tensives. Total peripheral resistance (t.p.r.) is increased initially (due to blockade of β mediated vasodilatation) and c.o. is reduced, so that there is little change in BP. With continued treatment, resistance vessels gradually adapt to chronically reduced c.o. and t.p.r. decreases—both systolic and diastolic BP fall. This is considered to be the most likely explanation of the antihypertensive action. Other mechanisms that may contribute are:
(i) Reduced NA release from sympathetic termi-nals due to blockade of β receptor mediated facilitation of the release process.
(ii) Decreased renin release from kidney ($β_1$ mediated): Propranolol causes a more marked fall in BP in hypertensives who have high or normal plasma renin levels and such patients respond at relatively lower doses than those with low plasma renin. However, pindolol does not decrease plasma renin activity but is an effective antihypertensive.
(iii) Central action reducing sympathetic out-flow. However, β blockers which penetrate brain poorly are also effective antihypertensives.

2. Respiratory tract Propranolol increases bronchial resistance by blocking dilator $β_2$ receptors. The effect is hardly discernible in normal individuals because sympathetic broncho-dilator tone is minimal. In asthmatics, however, the condition is consistently worsened and a severe attack may be precipitated.

3. CNS No overt central effects are produced by propranolol. However, subtle behavioural changes, forgetfulness, increased dreaming and nightmares have been reported with long-term use of relatively high doses.

Propranolol suppresses anxiety in short-term stressful situations, but this is due to peripheral rather than a specific central action (*see* p. 467).

4. Local anaesthetic Propranolol is as potent a local anaesthetic as lidocaine, but is not clinically used for this purpose because it causes irritation at the injected site.

5. Metabolic Propranolol blocks adrenergically induced lipolysis and consequent increase in plasma free fatty acid levels. Plasma triglyceride level and LDL/HDL ratio is increased during propranolol therapy. It also inhibits glycogenolysis in heart, skeletal muscles and in liver

(inconsistently), which occurs due to Adr release during hypoglycaemia—recovery from insulin action is delayed. Though there is no effect on normal blood sugar level, prolonged propranolol therapy may reduce carbohydrate tolerance by decreasing insulin release.

6. Skeletal muscle Propranolol inhibits adrenergically provoked tremor. This is a peripheral action exerted directly on the muscle fibres (through β_2 receptors). It tends to reduce exercise capacity by attenuating β_2 mediated increase in blood flow to the exercising muscles, as well as by limiting glycogenolysis and lipolysis which provide fuel to working muscles.

7. Eye Instillation of propranolol and some other β blockers reduces secretion of aqueous humor, i.o.t. is lowered. There is no consistent effect on pupil size or accommodation.

8. Uterus Relaxation of uterus in response to isoprenaline and selective β_2 agonists is blocked by propranolol. However, normal uterine activity is not significantly affected.

PHARMACOKINETICS

Propranolol is well absorbed after oral administration, but has low bioavailability due to high first pass metabolism in liver. Oral: parenteral dose ratio of up to 40:1 has been found. Interindividual variation in the extent of first pass metabolism is marked—equieffective oral doses vary considerably. Propranolol is lipophilic and penetrates into brain easily.

Metabolism of propranolol is dependent on hepatic blood flow. Chronic use of propranolol itself decreases hepatic blood flow: its own oral bioavailability is increased and its t½ is prolonged (by about 30%) on repeated administration. Bioavailability of propranolol is higher when it is taken with meals because food decreases its first pass metabolism. Higher bioavailability and prolongation of t½ is noted with high doses as well, because metabolism of propranolol is saturable.

A number of metabolites of propranolol have been found, of which the hydroxylated product has β blocking activity. The metabolites are excreted in urine, mostly as glucuronides. More than 90% of propranolol is bound to plasma proteins.

Dose: Oral—10 mg BD to 160 mg QID (average 40–160 mg/ day). Start with a low dose and gradually increase according to need; i.v.—2 to 5 mg injected over 10 min with constant monitoring. It is not injected s.c. or i.m. because of irritant property. INDERAL, CIPLAR 10, 40, 80 mg tab, 1 mg/ml inj., BETABLOC 10, 40 mg tab.

INTERACTIONS

1. Additive depression of sinus node and A-V conduction with digitalis and verapamil — cardiac arrest can occur. However, propranolol has been safely used with nifedipine.

2. Propranolol delays recovery from hypoglycaemia due to insulin and oral antidiabetics. Warning signs of hypoglycaemia mediated through sympathetic stimulation (tachycardia, tremor) are suppressed. In some cases BP rises due to unopposed α action of released Adr.

3. Phenylephrine, ephedrine and other α agonists present in cold remedies can cause marked rise in BP due to blockade of sympathetic vasodilatation.

4. Indomethacin and other NSAIDs attenuate the antihypertensive action of β blockers.

5. Cimetidine inhibits propranolol metabolism. However, the dose range of propranolol is wide, and this may not be clinically significant.

6. Propranolol retards lidocaine metabolism by reducing hepatic blood flow.

7. Propranolol increases bioavailability of chlorpromazine by decreasing its first pass metabolism.

ADVERSE EFFECTS AND CONTRAINDICATIONS

1. Propranolol can accentuate myocardial insufficiency and can precipitate CHF/edema by blocking sympathetic support to the heart, especially during cardiovascular stress. However, when compensation has been restored, careful

addition of certain β_1 blockers is now established therapy to prolong survival.

2. Bradycardia: resting HR may be reduced to 60/min or less. Patients of sick sinus are more prone to severe bradycardia.

3. Propranolol worsens chronic obstructive lung disease, can precipitate life-threatening attack of bronchial asthma: contraindicated in asthmatics.

4. Propranolol exacerbates variant (vasospastic) angina due to unopposed α mediated coronary constriction. In some patients, even classical angina may be worsened if ventricular dilatation and asynergy of contraction occurs—specially with high doses.

5. Carbohydrate tolerance may be impaired in prediabetics.

6. Plasma lipid profile is altered on long term use: total triglycerides and LDL-cholesterol tend to increase while HDL-cholesterol falls. This may enhance risk of coronary artery disease. Cardioselective β blockers and those with intrinsic sympathomimetic activity have little/no deleterious effect on blood lipids.

7. Withdrawal of propranolol after chronic use should be gradual, otherwise rebound hypertension, worsening of angina and even sudden death can occur. This is due to supersensitivity of β receptors occurring as a result of long-term reduction in agonist stimulation.

8. Propranolol is contraindicated in partial and complete heart block: arrest may occur.

9. Tiredness and reduced exercise capacity: due to blunting of β_2 mediated increase in blood flow to the exercising muscles as well as attenuation of glycogenolysis and lipolysis.

10. Cold hands and feet, worsening of peripheral vascular disease are noticed due to blockade of vasodilator β_2 receptors.

11. Side effects not overtly due to β blockade are—g.i.t. upset, lack of drive, nightmares, forgetfulness, rarely hallucinations. Male patients more frequently complain of sexual distress.

OTHER β BLOCKERS

A number of β blockers have been developed having some special features. Their comparative properties are presented in Table 10.2. The associated properties alongwith their significance can be summarized as:

Cardioselectivity (in metoprolol, atenolol, acebutolol, bisoprolol, nebivolol).

These drugs are more potent in blocking cardiac (β_1) than bronchial (β_2) receptors. However, selectivity is only relative and is lost at high doses. Their features are:

1. Lower propensity to cause bronchoconstriction, but even these drugs should usually be avoided in asthmatics and COPD patients. However, a coexisting cardiac condition may warrant their use, which may be initiated at low dose and under supervision.

2. Less interference with carbohydrate metabolism and less inhibition of glycogenolysis during hypoglycaemia—safer in diabetics.

However, tachycardia in response to hypoglycaemia is blocked.

3. Lower incidence of cold hands and feet, less chances of precipitating Raynaud's phenomenon.

4. No/less deleterious effect on blood lipid profile.

5. Ineffective in suppressing essential tremor (it occurs through β_2 action on muscle fibres).

6. Less liable to impair exercise capacity.

Partial agonistic (intrinsic sympathomimetic) action (in pindolol, celiprolol, acebutolol). These drugs themselves activate β_1 and/or β_2 receptors submaximally. The benefits of this property are controversial.

1. Bradycardia and depression of contractility at rest are not prominent, but exercise tachycardia is blocked; may be preferred in those prone to severe bradycardia (elderly patients; sick sinus) or with low cardiac reserve.

2. Withdrawal is less likely to exacerbate hypertension or angina; continued agonistic action on β receptors (of the drug itself) prevents development of supersensitivity.

3. Plasma lipid profile is not/less worsened.

4. Not effective in migraine prophylaxis—they dilate cerebral vessels.

5. Not suitable for secondary prophylaxis of MI.

TABLE 10.2	Comparative properties of β blockers								
β–BLOCKER	Potency (on β₁)	Partial agonistic action	Membrane stabilizing action	Lipid solubility	Daily dose (mg)	Oral bioavailability (%)	First pass metabolism	Major route of elimination	Plasma t½(hours)
NONSELECTIVE									
1. Propranolol	1	–	++	+++	40–480	~30	Yes	Hep.*	3–5
2. Sotalol	1/3	–	–	±	160–480	~60	No	Ren.!+Hep.	6–12
3. Timolol	6	–	–	++	10–40	50–75	Partial	Ren.+Hep.	4–5
4. Pindolol	6	+++	±	+	10–30	90	No	Ren.+Hep.	3–4
CARDIOSELECTIVE									
1. Metoprolol	1	–	±	++	100–400	40–50	Yes	Hep.	3–6
2. Atenolol	1	–	–	–	25–100	50–60	No	Ren.	6–9
3. Acebutolol	1/3	+	+	±	400–1200	40–60	Yes	Hep.+Ren.	3–4
4. Bisoprolol	6	–	–	–	2.5–10	80	No	Hep.+Ren.	9–12
α + β BLOCKER									
1. Labetalol	1/3	+	+	±	300–600	~30	Yes	Hep.	4–6

*Hep—Hepatic metabolism; !Ren.—Renal excretion

Membrane stabilizing activity (in propranolol, oxprenolol, acebutolol). This activity is claimed to contribute to the antiarrhythmic action, but appears to be significant only at high doses.

Lipid insolubility (atenolol, celiprolol, bisoprolol, sotalol)
1. They are less likely to produce sleep disturbances and nightmares.
2. They are incompletely absorbed orally, but do not undergo first pass metabolism and are primarily excreted unchanged in urine: are longer acting (t½ 6–20 hours) and tend to be effective in a narrow dose range. In contrast, the lipid soluble agents are primarily metabolized in liver and have shorter t½ (2–6 hours).

Salient features of important β blockers are given below.

1. Sotalol Nonselective β blocker with low lipid solubility. It has additional cardiac rectifier K⁺ channel blocking and class III antiarrhythmic property.
SOTAGARD 40, 80 mg tab.

2. Timolol It is the β blocker preferred for topical use in eye for glaucoma (*see* p. 153).

Orally it is a potent β blocker—has been used in hypertension, angina and prophylaxis of myocardial infarction.

Betaxolol, Levobunolol, Cartiolol and *Metipranolol* are β blockers employed exclusively for topical application to the eye (*see* p. 154).

3. Pindolol A potent β blocker with prominent intrinsic sympathomimetic activity. It has been used primarily as antihypertensive: may be advantageous in patients who develop marked bradycardia with propranolol. Chances of rebound hypertension on withdrawal are also less. The effective dose range is rather narrow.
PINADOL 5 mg tab, VISKEN 10, 15 mg tab.

4. Metoprolol It is the prototype of cardioselective (β₁) blockers; nearly 50 times higher dose is needed to block isoprenaline induced vasodilatation. Some measure of inverse agonistic activity on β₁ receptors has also been demonstrated. It is less likely to worsen asthma, but is not entirely safe. It may be preferred in diabetics receiving insulin or oral hypoglycaemics. Patients who complain of cold hands and feet while on propranolol do better on metoprolol.

First pass metabolism of metoprolol is less marked than propranolol, but 90% or more is

ultimately hydroxylated by CYP2D6 before excretion. There are slow and fast hydroxylators of metoprolol (CYP2D6 alleles); the former may require a lower dose.

Side effects of metoprolol are milder. It is generally given orally for hypertension, angina and CHF, but i.v. injection (5–15 mg) has been used in myocardial infarction provided brady-cardia is absent.

BETALOC 25, 50, 100 mg tab, 5 mg/ml inj. LOPRESOR, METOLAR 50, 100 mg tab.

S(–) Metoprolol is the active enantiomer, now available as a single enantiomer product. It is to be used at half the dose as the racemate.
Dose: 12.5–50 mg OD–BD.
METPURE-XL 12.5, 25, 50 mg extended release tabs.

5. Atenolol A relatively selective β_1 blocker having low lipid solubility. It is incompletely absorbed orally, but first pass metabolism is not significant. Because of longer duration of action, once daily dose is often sufficient. Side effects related to CNS action are less likely. No deleterious effects on lipid profile have been noted. Effective dose for most individuals falls in a narrow range. It is one of the most commonly used β blockers for hypertension and angina.

BETACARD, ATEN, TENORMIN 25, 50, 100 mg tab.

S(–) Atenolol This pure active enantiomer is effective at half the dose and may be better tolerated.
Dose: 12.5–50 mg OD;
ATPURE, ADBETA 12.5, 25, 50 mg tabs.

6. Acebutolol Another cardioselective agent with significant partial agonistic and membrane stabilizing properties. Effect on resting heart rate is less. The side effect profile is like that of metoprolol. Acebutolol is rapidly metabolized to an active metabolite diacetolol which is primarily excreted by kidney and has a longer $t\frac{1}{2}$ (8–12 hours). As such, a single daily dose is sufficient in many patients.

SECTRAL 200, 400 mg tab., 10 mg/2 ml amp. Intravenous dose for arrhythmias 20–40 mg.

7. Bisoprolol A cardioselective β blocker lacking intrinsic sympathomimetic activity;

suitable for once daily administration in angina, hypertension and CHF.
CONCOR, CORBIS 5 mg tab; ½ to 2 tab OD.

8. Esmolol It is an ultrashort acting β_1 blocker devoid of partial agonistic or membrane stabili-zing actions. It is inactivated by esterases in blood; plasma $t\frac{1}{2}$ is < 10 min; action disappears 15–20 min after terminating i.v. infusion—degree of β blockade can be titrated by regulating the rate of infusion. Rapid onset, short lasting fall in BP attends i.v. infusion of esmolol.

A loading dose of 0.5 mg/kg is given followed by 0.05–0.2 mg/kg/min infusion. It has been used to terminate supraventricular tachycardia, episo-dic atrial fibrillation or flutter, arrhythmia during anaesthesia, to reduce HR and BP during and after cardiac surgery, and in early treatment of myocardial infarction.
MINIBLOCK 100 mg/10 ml, 250 mg/10 ml inj.

9. Celiprolol It is a selective β_1 blocker having additional weak β_2 agonistic activity which reduces vascular resistance and holds promise of safety in asthmatics. Nonadrenoceptor mediated vasodilatation (due to NO production) adds to its antihypertensive action.
Dose: 200–600 mg OD; CELIPRES 100, 200 mg tab.

10. Nebivolol This highly selective β_1 blocker also acts as a NO donor, produces vasodilatation and has the potential to improve endothelial function, which may delay atherosclerosis. Absence of deleterious effect on plasma lipids and on carbohydrate metabolism is another advantage. In contrast to older β blockers, hypo-tensive response to nebivolol has a rapid onset. It has been used in hypertension and CHF.
Dose: 5 mg (elderly 2.5 mg) OD;
NEBICARD 2.5, 5 mg tabs, NODON 5 mg tab.

USES

1. *Hypertension* β blockers are relatively mild antihypertensives. All agents, irrespective of asso-ciated properties, are nearly equally effective. They are one of the first choice drugs because of good patient acceptability and cardioprotective potential (*see* Ch. 40).

2. *Angina pectoris* All β blockers benefit angina of effort. Taken on a regular schedule they decrease frequency of attacks and increase exercise tolerance. High doses, however, may worsen angina in some patients by increasing ventricular size and reducing coronary flow. β blockers are not suitable for variant (vasospastic) angina (*see* Ch. 39).

3. *Cardiac arrhythmias* β blockers (mainly propranolol) suppress extrasystoles and tachycardias, especially those mediated adrenergically (during anaesthesia, digitalis induced)—may be used i.v. for this purpose. Propranolol controls ventricular rate in atrial fibrillation and flutter, but only occasionally restores sinus rhythm. Esmolol is an alternative drug for paroxysmal supraventricular tachycardia (*see* Ch. 38).

4. *Myocardial infarction (MI)* In relation to MI, β blockers have been used for two purposes: (a) *Secondary prophylaxis of MI:* There is now firm evidence of benefit. Long-term use after recovery from MI has been found to decrease subsequent mortality by 20%. They may act by:
   (i) Preventing reinfarction
   (ii) Preventing sudden ventricular fibrillation at the subsequent attack of MI.

High risk patients (those who had large infarcts) should be put on β blockers (if there are no haemodynamic contraindications) for at least 2 years. β blockers with partial agonistic action are less suitable for this purpose.
(b) *Myocardial salvage during evolution of MI:* Administered i.v. within 4–6 hours of an attack followed by continued oral therapy. β blockers—
   (i) May limit infarct size by reducing O_2 consumption—marginal tissue which is partially ischaemic may survive.
   (ii) May prevent arrhythmias including ventricular fibrillation.

However, β blockers can be given to only those patients not in shock or cardiac failure and who have heart rate > 50/min with not higher than first degree heart block (P-R interval < 0.24 sec). In megatrials such therapy has been found to reduce mortality by 20–25%.

5. *Congestive heart failure* Although β blockers can acutely worsen heart failure, several studies have reported beneficial haemodynamic effects of certain β blockers including *metoprolol, bisoprolol, nebivolol, carvedilol* over long-term in selected patients with dilated cardiomyopathy. Introduced gradually and maintained for long term, these drugs retard the progression of CHF and prolong life. The benefit may result from antagonism of deleterious effects of sympathetic overactivity (invoked reflexly by heart failure) on myocardium. Overactivation of cardiac $β_1$ receptors has been found to exert toxic effects on the heart by accelerating myocyte apoptosis and promoting functionally unfavourable remodeling. One of the above named $β_1$ blockers, used appropriately along with other measures, is now established as standard therapy for most mild to moderate CHF patients. However, they should not be given to patients with marked fluid retention and to those requiring i.v. vasodilators or i.v. inotropic drugs (*see* Ch. 37).

6. *Dissecting aortic aneurysm* β blockers help by reducing cardiac contractile force and aortic pulsation. Nitroprusside infusion is often added.

7. *Pheochromocytoma* β blockers may be used to control tachycardia and arrhythmia, but should never be administered unless an α blocker has been given before, otherwise dangerous rise in BP can occur. They suppress cardiomyopathy caused by excess CAs.

8. *Thyrotoxicosis* Propranolol rapidly controls the sympathetic symptoms (palpitation, nervousness, tremor, fixed stare, severe myopathy and sweating) without significantly affecting thyroid status. It also inhibits peripheral conversion of T_4 to T_3 and is highly valuable during thyroid storm. Major use, however, is preoperatively and while awaiting response to antithyroid drugs/radioactive iodine.

9. *Migraine* Propranolol is the most effective drug for chronic prophylaxis of migraine (*see* p. 179).

10. *Anxiety* Propranolol exerts an apparent antianxiety effect, especially under conditions which provoke nervousness and panic, e.g. examination, unaccustomed public appearance, etc. This is probably due to blockade of peripheral manifestations of anxiety (palpitation, tremor) which have a reinforcing effect. Propranolol is largely ineffective in anxiety neurosis, but may benefit the somatic symptoms.

11. *Essential tremor* Nonselective $\beta_1 + \beta_2$ blockers have now an established place in treating essential tremor. However, they do not benefit parkinsonian tremor.

12. *Glaucoma* Ocular β blockers are widely used for chronic simple (wide angle) glaucoma; also used as adjuvant in angle closure glaucoma (*see* later in this Ch.).

13. *Hypertrophic obstructive cardiomyopathy* The subaortic region is hypertrophic. Forceful contraction of this region under sympathetic stimulation (exercise, emotion) increases outflow resistance which has incapacitating haemodynamic consequence. β blockers improve c.o. in these patients during exercise by reducing left ventricular outflow obstruction, though they have little effect while at rest.

$\alpha + \beta$ ADRENERGIC BLOCKERS

Labetalol It is the first adrenergic antagonist capable of blocking both α and β receptors. There are 4 diastereomers of labetalol, each of which has a distinct profile of action on subtypes of α and β receptors. The commercial preparation has equal parts of each diastereomer and displays $\beta_1 + \beta_2 + \alpha_1$ blocking as well as weak β_2 agonistic activity. The β blocking potency is about 1/3 that of propranolol, while α blocking potency is about 1/10 of phentolamine.

Labetalol is 5 times more potent in blocking β than α receptors. As such, effects of a low dose resemble those of propranolol alone while at high dose they are like a combination of propranolol and prazosin. Fall in BP (both systolic and diastolic) is due to α_1 and β_1 blockade as well as β_2 agonism

(vasodilatation). Relatively high doses reduce both c.o. and t.p.r. Heart rate is unchanged or slightly decreased. In contrast to propranolol, limb blood flow increases with labetalol. It has also been shown to inhibit NA uptake by adrenergic nerve endings.

Labetalol is orally effective but undergoes considerable first pass metabolism.

It is a moderately potent hypotensive and is especially useful in pheochromocytoma and clonidine withdrawal; can also be used in essential hypertension.

Most important side effect is postural hypotension, but this is significant only in some patients. Failure of ejaculation and other side effects of α and β blockers can also occur, but plasma lipid levels are not altered. Rashes and liver damage have been reported.

Dose: Start with 50 mg BD, increase to 100–200 mg TDS oral. In hypertensive emergencies 20–40 mg i.v. every 10 min till desired response is obtained.
NORMADATE 50, 100, 200 mg tab, LABESOL, LABETA 50 mg tab, 20 mg 4 ml amp.

Carvedilol It is a $\beta_1 + \beta_2 + \alpha_1$ adrenoceptor blocker; produces vasodilatation due to α_1 blockade as well as calcium channel blockade, and has antioxidant property. It has been used in hypertension and is the β blocker especially employed as cardioprotective in CHF. Oral bioavailability of carvedilol is 30%. It is primarily metabolized and has a t½ of 6–8 hrs.

CHF: Start with 3.125 mg BD for 2 weeks, if well tolerated gradually increase to max. of 25 mg BD.

Hypertension/angina: 6.25 mg BD initially, titrate to max. of 25 mg BD.
CARVIL, CARLOC, CARVAS 3.125, 6.25, 12.5, 25 mg tabs; ORICAR 12.5, 25 mg tabs.

DRUGS FOR GLAUCOMA

Glaucoma is a group of diseases characterized by a progressive form of optic nerve damage. This is generally but not necessarily associated with raised (>21 mmHg) intraocular tension (i.o.t), but the etiology is unknown and there are many risk factors. The chief therapeutic measure is to lower i.o.t., either by reducing secretion of aqueous

humor or by promoting its drainage. Lowering of i.o.t. retards progression of optic nerve damage even in normal/low i.o.t. glaucoma.The site of formation and pathway of drainage of aqueous humor as well as sites of action of antiglaucoma drugs is illustrated in Fig. 10.1. Major amount of aqueous (~90%) drains through the *trabecular route*, while ~10% fluid passes into the connective tissue spaces within the ciliary muscle—then *via* suprachoroid into episcleral vessels *(uveoscleral outflow)*. Glaucoma is seen in *two* principal clinical forms:

A. Open angle (wide angle, chronic simple) glaucoma

It is probably a genetically predisposed degenerative disease affecting patency of the trabecular meshwork which is gradually lost past middle age. The i.o.t. rises insidiously and progressively. Ocular hypotensive drugs are used on a long term basis and constitute the definitive treatment in majority of cases. The mode of ocular hypotensive action of topical antiglaucoma drugs is summarized in Table 10.3.
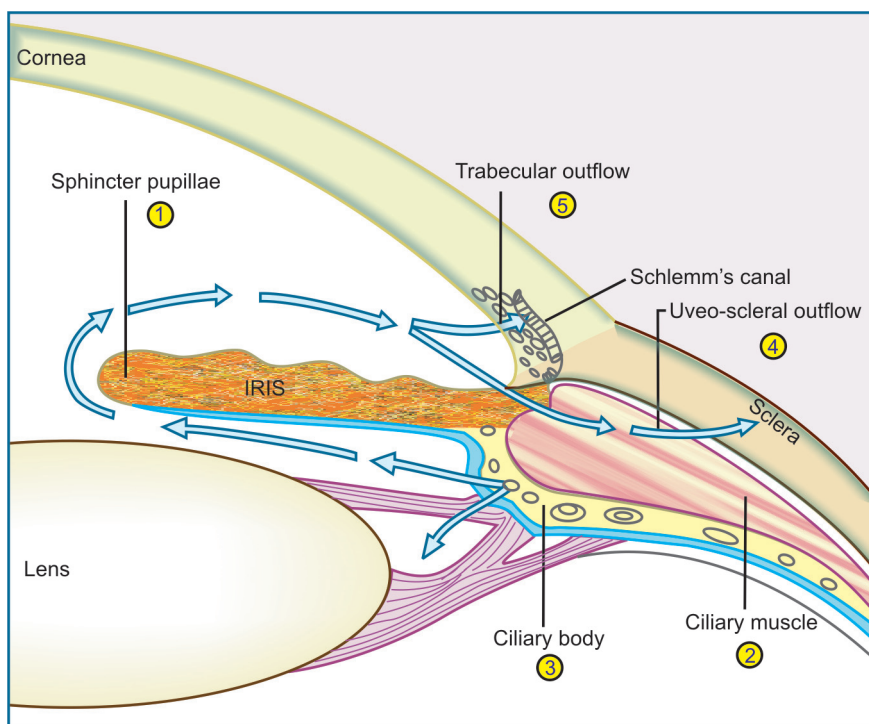

Fig. 10.1: Illustration of aqueous humor dynamics and the sites of action of ocular hypotensive drugs

(1)   Site of action of miotics in angle closure glaucoma: contraction of sphincter pupillae removes pupillary block and reverses obliteration of iridocorneal angle

(2)   Site of action of miotics in open angle glaucoma: contraction of ciliary muscle pulls on scleral spur and improves trabecular patency

(3)   Site of action of (a) β blockers (b) α_1 agonists (c) α_2 agonists (d) carbonic anhydrase inhibitors: all reduce aqueous secretion by ciliary body

(4)   Site of action of prostaglandins and adrenaline (α agonist action): increase uveoscleral outflow by altering permeability and/or pressure gradients

(5)   Site of action of adrenaline (β_2 agonist action): possibly increases aqueous conductivity of trabecular filtering cells

1. β Adrenergic blockers

Topical β blockers have been the first line drugs till recently, but PG $F_{2\alpha}$ analogues are the preferred drugs now. In contrast to miotics, the β blockers donot affect pupil size, tone of ciliary muscle or outflow facility, but lower i.o.t. by reducing aqueous formation. This probably results from down regulation of adenylylcyclase due to β_2 receptor blockade in the ciliary epithelium (*see* Fig. 10.2) and a secondary effect due to reduction in ocular blood flow. They are as effective as miotics and produce less ocular side effects. Ocular β blockers are lipophilic with high ocular capture (to reduce systemic effects) and have no/weak local anaesthetic activity (to avoid corneal hypoesthesia and damage).

Ocular side effects of β blockers　These are generally mild and infrequent—stinging, redness and dryness of eye, corneal hypoesthesia, allergic blepharoconjunctivitis and blurred vision.
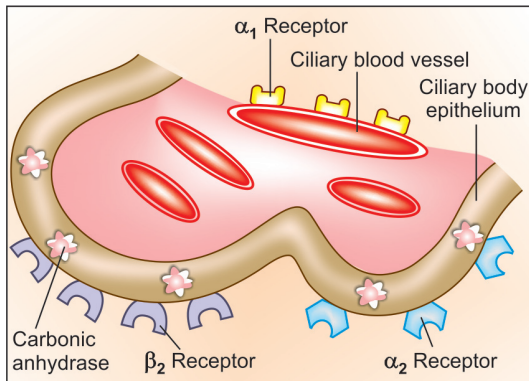

Fig. 10.2: Location of α_1, α_2 and β_2 adrenergic receptors and of carbonic anhydrase enzyme (molecules which are targets of drug action for reducing aqueous formation) in the processes of the ciliary body
α_1 adrenoceptors constrict ciliary vessels and reduce aqueous production: are activated by adrenaline.
α_2 adrenoceptors located on ciliary epithelium reduce aqueous secretion: are activated by adrenaline/apraclonidine/brimonidine.
β_2 adrenoceptors located on ciliary epithelium enhance aqueous secretion *via* increased cAMP. Their blockade by timolol/betaxolol reduces secretion.
Carbonic anhydrase present within ciliary epithelial cells generates HCO_3^- ion which is secreted into aqueous humor. Acetazolamide/dorzolamide inhibit it and reduce aqueous secretion.

Advantages of topical β blockers over miotics
• No change in pupil size: no diminution of vision in dim light and in patients with cataract • No induced myopia which is especially troublesome in young patients • No headache/brow pain due to persistent spasm of iris and ciliary muscles • No fluctuations in i.o.t. as occur with pilocarpine drops • Convenient twice/once daily application sufficient

Systemic adverse effects　These are the major limitations in the use of ocular β blockers, and occur due to absorption through nasolacrimal duct. Life-threatening bronchospasm has been reported in asthmatic and COPD patients. Bradycardia, accentuation of heart block and CHF are likely, especially in the elderly. In fact all adverse effects and contraindications of systemic β blocker therapy (*see* p. 147) apply to ocular β blockers as well. Systemic adverse effects can be minimized by applying mild pressure on the inner canthus of the eye for about 5 min. after instilling the eyedrop to prevent entry of the drug into naso-lacrimal duct from where it is mainly absorbed.

Timolol　It is the prototype of ocular β blockers; is nonselective (β_1 + β_2) and has no local anaesthetic or intrinsic sympathomimetic activity. The ocular hypotensive action (20–35% fall in i.o.t.) becomes evident within 1 hour and lasts for ~12 hours. After chronic dosing, the action is smooth and well sustained. Some effect on i.o.t. persists for 1–2 weeks following discontinuation. This feature, in contrast to pilocarpine drops, gives a high level of clinical safety, i.e. 1 or 2 missed doses will not affect i.o.t. control. However, ~30% cases of open angle glaucoma fail to achieve the desired level of i.o.t. with timolol alone, and may need additional medication.

GLUCOMOL, OCUPRES, IOTIM, LOPRES 0.25% and 0.5% eye drops; start with 0.25% drops BD, change to 0.5% drops in case of inadequate response. TIMOLAST 0.5% as gelforming eyedrop for OD use.

Betaxolol　It is β_1 selective blocker offering the advantage of less bronchopulmonary and probably less cardiac, central and metabolic side

effects. In addition, it appears to exert a protective effect on retinal neurones independent of i.o.t. lowering, by blocking some Ca^{2+} channels and reducing Na^+/Ca^{2+} influx. This action is more prominent in betaxolol than in timolol. However, betaxolol is less efficacious in lowering i.o.t. than timolol, because ocular β receptors are predominantly of the β_2 subtype. Transient stinging and burning in the eye is more common with it. Most ophthalmologists prefer to start with betaxolol and change over to timolol (or a similar drug) only if i.o.t. control is insufficient or there is local intolerance to betaxolol.

OPTIPRESS, IOBET, OCUBETA 0.5% eye drops; 1 drop in each eye BD.

Levobunolol   It has been introduced as a once daily alternative to timolol. The ocular and systemic effects are very similar to timolol except for longer duration of action.

BETAGAN 0.5% ophthalmic soln., 1 drop OD.

Carteolol and *Metipranolol* are the other ocular β blockers.

2. α Adrenergic agonists

Dipivefrine   It is a prodrug of Adr; penetrates cornea and is hydrolysed by the esterases present there into Adr, which itself has poor corneal penetration and causes ocular smarting, reactive hyperemia. The released Adr (from dipivefrine) lowers i.o.t. by augmenting uveoscleral outflow, β_2 receptor mediated increase in hydraulic conductivity of trabecular filtering cells, as well as by reducing aqueous formation ($\alpha_1 + \alpha_2$ receptor mediated). Though better tolerated and longer acting than Adr, dipivefrine still produces significant ocular burning and other side effects. It is infrequently used for add on therapy.

PROPINE 0.1% eye drop; 1 drop in each eye BD.

Apraclonidine   It is a polar clonidine congener which does not cross blood-brain barrier, but applied topically (0.5–1%) it lowers i.o.t. by ~25%. It decreases aqueous production by primary α_2 and subsidiary α_1 action in the ciliary body. Itching, lid dermatitis, follicular conjunctivitis, mydriasis, eyelid retraction, dryness of mouth and nose are common side effects. Its use is restricted to short

TABLE 10.3	Mode of action of ocular hypotensive drugs		
Drug/class	*Aqueous secretion*	*Trabecular outflow*	*Uveoscleral outflow*
1. β-blockers (Timolol)	↓	–	–
2. Adrenaline/ Dipivefrine	↓	↑	↑
3. Brimonidine/ apraclonidine	↓	–	↑
4. Prostaglandins (Latanoprost)	–	↑	↑
5. Miotics (Pilocarpine)	–	↑	–
6. Carbonic anhydrase inhibitors	↓	–	–

term control of spikes of i.o.t. after laser trabeculoplasty or iridotomy.

ALFADROPS DS 1% eyedrops.

Brimonidine   This clonidine congener is more α_2 selective and more lipophilic than apraclonidine. It lowers i.o.t. by 20–27% by reducing aqueous production and by increasing uveoscleral flow. Peak effect on i.o.t. occurs after 2 hours. Allergic conjunctivitis and other ocular side effects are similar to but less frequent than with apraclonidine. Because of weaker α_1 action, side effects like mydriasis, eyelid retraction, conjunctival blanching followed by hyperemia are less prominent, but dry mouth, sedation and a small fall in BP have been noted.

Brimonidine is indicated both for short-term (prophylaxis of i.o.t. spikes post laser/post surgery) as well as long-term use in glaucoma. It is generally used for add on therapy only.

ALPHAGAN-P, BRIMODIN-P 0.15% eyedrops, IOBRIM 0.2% eyedrops; 1 drop in each eye TDS.

3. Prostaglandin analogues

Low concentration of $PGF_{2\alpha}$ was found to lower i.o.t without inducing ocular inflammation. It acts by increasing uveoscleral outflow, possibly by increasing permeability of tissues in ciliary muscle or by an action on episcleral vessels. An effect on trabecular outflow has also been demonstrated, but is less marked. Ciliary body COX-2 has been found

to be down regulated in wide angle glaucoma indicating a physiological role of PGs in aqueous humor dynamics.

Latanoprost Instilled in the eye, this $PGF_{2\alpha}$ derivative has shown efficacy similar to timolol (i.o.t. reduction by 25–35%) and the effect is well sustained over long-term. It reduces i.o.t. in normal pressure glaucoma also. Though ocular irritation and pain are relatively frequent, no systemic side effects are reported. Blurring of vision, increased iris pigmentation, thickening and darkening of eyelashes have occurred in some cases. Macular edema can develop during treatment with any $PGF_{2\alpha}$ analogue, especially in aphakic patients; a watch should be kept to detect it early.

Because of good efficacy, once daily application and absence of systemic complications, PG analogues have become the first choice drugs for open angle glaucoma. High cost is a disadvantage.
LACOMA, XALATAN, LATOPROST, 0.005% eyedrops, one drop in each eye OD in the evening; LACOMA-T LAPROST PLUS, LATOCHECK-T eyedrops with timolol 0.5% eyedrops. (To be stored in cold)

Travoprost Another selective FP-prostanoid receptor agonist which lowers i.o.t. mainly by increasing uveoscleral outflow and a minor effect on trabecular outflow. The effect starts within 2 hours, peaks at 12 hours and lasts for 24 hours or more. The i.o.t. lowering efficacy and side effects are comparable to latanoprost. Some patients not responding well with one may respond to the other.
TRAVATAN 0.004% eyedrops. One drop in each eye in the evening; refrigeration of the eyedrop is not required; TRAVACOM 0.004% with timolol 0.5% eyedrop.

Bimatoprost A synthetic prostamide derivative found to be equally or more effective than latanoprost in lowering i.o.t. Ocular side effects are also similar, but some patients may tolerate it better.
LUMIGAN, CAREPROST 0.3% eyedrops; one drop in each eye OD in the evening. The eyedrop need not be stored in refrigerator.

4. Carbonic anhydrase inhibitors
Acetazolamide (*see* Ch. 41) Oral treatment with acetazolamide (0.25 g 6–12 hourly) reduces aqueous formation by limiting generation of

bicarbonate ion in the ciliary epithelium. It is used to supplement ocular hypotensive drugs for short term indications like angle closure, before and after ocular surgery/laser therapy. Systemic side effects—paresthesia, anorexia, hypokalaemia, acidosis, malaise and depression restrict long-term use to few cases in which target i.o.t. is not achieved even by concurrent use of 2–3 topical drugs.

Dorzolamide (2% eyedrops BD-TDS) It is a topically useful carbonic anhydrase inhibitor developed to circumvent systemic side effects of acetazolamide. It lowers i.o.t. by ~20%; somewhat less efficacious than timolol. Ocular stinging, burning, itching, corneal edema and bitter taste are the usual side effects. Systemic adverse effects are also possible. Dorzolamide is used only as add on drug to topical β blockers/PG analogues, or when these drugs are contraindicated.
DORTAS, DORZOX 2% eyedrops.

Brinzolamide is another ocular carbonic anhydrase inhibitor.

5. Miotics: Till the 1970s topical pilocarpine and/or antiChEs were the standard antiglaucoma drugs (*see* Ch. 7). However, because of several drawbacks (*see* box on p. 153), they are now used only as the last option. In open angle glaucoma, they lower i.o.t. by increasing ciliary muscle tone thereby improving patency of trabeculae.

The current approach to treatment of open angle glaucoma can be summarized as—start monotherapy with latanoprost or a topical β blocker; if target i.o.t. is not attained, either change over to the alternative drug or use both the above concurrently. Brimonidine/dorzolamide (occasionally dipivefrine) are used only when there are contraindications to PG analogues and/or β blockers, or to supplement their action. Topical miotics and oral acetazolamide are added only as the last resort.

B. Angle closure (narrow angle, acute congestive) glaucoma

It occurs in individuals with a narrow iridocorneal angle and shallow anterior chamber. The i.o.t.
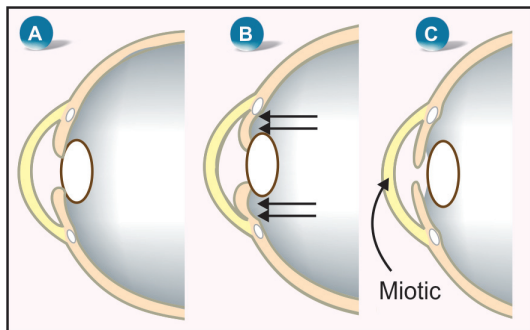
Fig. 10.3: Development of angle closure glaucoma and its reversal by miotic

A. Mydriasis occurs in an eye with narrow iridocorneal angle and iris makes contact with lens blocking passage of aqueous from posterior to anterior chamber.
B. Pressure builds up behind the iris which bulges forward and closes the iridocorneal angle thus blocking aqueous outflow.
C. Miotic makes the iris thin and pulls it away from the lens removing the pupillary block and restoring aqueous drainage

remains normal until an attack is precipitated, usually by mydriasis (Fig. 10.3A,B). The i.o.t. rises rapidly to very high values (40–60 mmHg). It is an emergent condition with marked congestion of eyes and severe headache. Failure to lower i.o.t. quickly may result in loss of sight.

Vigorous therapy employing various measures to reduce i.o.t. is instituted.
1. *Hypertonic mannitol (20%) 1.5–2 g/kg or glycerol (10%):* infused i.v. decongest the eye by osmotic action. A retention enema of 50% glycerine is also some times used.
2. *Acetazolamide*: 0.5 g i.v. followed by oral twice daily is started concurrently.
3. *Miotic:* Once the i.o.t. starts falling due to the above i.v. therapy, pilocarpine 1–4% is instilled every 10 min initially and then at longer intervals. Contraction of sphincter pupillae changes the direction of forces in the iris to

☞ PROBLEM DIRECTED STUDY

10.1　A 70-year-male presented with the complaints of weak stream of urine, sense of incomplete bladder voiding, urinary frequency and nocturia. After physical examination and ultrasound, he was diagnosed to have developed benign prostatic hypertrophy and was prescribed:

Tab. Terazosin 5 mg, one tab daily at bed time.

He took the medicine as advised and went off to sleep. At night, when he got up to pass urine, he felt giddy and fainted. On being laid flat on the bed, he regained consciousness within 2 minutes. Later, he was gradually propped up on the bed to the sitting position and then got up slowly and walked without any problem.

(a) What is the rationale of prescribing terazosin to this patient?
(b) What is the likely explanation for the fainting attack?
(c) What precautions could have avoided the fainting episode?

10.2 A lady aged 55 years was brought at night to the hospital emergency with severe breathlessness and wheezing. Chest auscultation revealed marked bronchoconstriction. She was managed with 100% O_2 inhalation and nebulized salbutamol + ipratropium bromide. The asthmatic attack was controlled in about 6 hours. Next day, history taking revealed that she was having mild episodic asthma off and on, but never had such a severe attack. Day before she had visited an ophthalmologist for visual difficulty and frontal headache. The intraocular pressure was measured to be 24 and 25 mmHg in right and left eye respectively. She was prescribed:

Timolol 0.5% eyedrops in each eye twice a day.

(a) What is the most likely explanation for the precipitation of severe attack of asthma?
(b) How could such a complication be avoided?
(see Appendix-1 for solutions)

lessen its contact with the lens and spreads the iris mass centrally → pupillary block is removed and iridocorneal angle is freed (Fig. 10.3C). However, when i.o.t. is very high, the iris muscle fails to respond to miotics; tension should be reduced by other measures before miotics can act.

4. *Topical β blocker:* Timolol 0.5% is instilled 12 hourly in addition.

5. *Apraclonidine* (1%)/latanoprost 0.005% instillation may be added.

Drugs are used only to terminate the attack of angle closure glaucoma. Definitive treatment is surgical or laser iridotomy. Few cases, who have chronic narrow angle glaucoma, may be treated with a miotic/other ocular hypotensive drug for long periods, but often surgery/laser therapy is ultimately required.

SECTION 3

AUTACOIDS AND RELATED DRUGS

Autacoid This term is derived from Greek: *autos*—self, *akos*—healing substance or remedy.

These are diverse substances produced by a *wide variety of cells* in the body, having intense biological activity, but generally *act locally* (e.g. within inflammatory pockets) at the site of synthesis and release.

They have also been called 'local hormones'. However, they differ from 'hormones' in two important ways—hormones are produced by *specific cells,* and are transported through circulation to act on *distant target tissues*.

Autacoids are involved in a number of physiological and pathological processes (especially reaction to injury and immunological insult). Some autacoids, in addition, serve as transmitters or modulators in the nervous system, but their role at many sites is not precisely known. A number of useful drugs act by modifying their action or metabolism. The classical autacoids are—

Amine autacoids Histamine, 5-Hydroxytryptamine (Serotonin)

Lipid derived autacoids Prostaglandins, Leukotrienes, Platelet activating factor

Peptide autacoids Plasma kinins (Bradykinin, Kallidin), Angiotensin

In addition, cytokines (interleukins, TNFα, GM-CSF, etc.) and several peptides like gastrin, somatostatin, vasoactive intestinal peptide and many others may be considered as autacoids.