

General and ocular pharmacology

- Introduction
- Pharmacokinetics: drug trafficking in the body
- Pharmacodynamics: drug handling by the body
- Drug–receptor interactions
- Ocular pharmacology: drug handling by cells and tissues of the eye
- Delivery methods of ocular medication
- Reconstituting the tear film
- Ocular drugs and the autonomic nervous system
- Clinical control of intraocular pressure exploits the adrenergic system
- The histaminergic system: histamine is released from conjunctival mast cells during allergic reactions
- Eicosanoids affect multiple ocular functions
- Serotonin: a potent neurotransmitter
- Glucocorticoids
- Immunosuppressant agents: combating ocular inflammatory disease
- Local anaesthetics: an integral part of ophthalmic examination and surgery
- Ocular toxicity from systemic administration of drugs

Introduction

This chapter covers the basic principles of clinical pharmacology, with particular reference to drugs used in the management of ophthalmic disorders, methods of ocular drug delivery, and the interactions of drugs and the eye. Although it is generally thought that the medical management of ocular disease is mainly administered through topical therapeutic agents, many systemic drugs and agents are also used. These include diuretics for the control

of intraocular pressure, immunosuppressants for control of intraocular inflammatory conditions and antimicrobials for control of infection. Therefore, basic pharmacological principles (pharmacokinetics and pharmacodynamics) are important to ophthalmologists. The basic pharmacology of systemic therapy, including receptor–drug interactions, is reviewed before discussing the more specific topical and systemic therapies in the treatment of ophthalmic disorders.

Pharmacokinetics: drug trafficking in the body

BASIC CONCEPTS

Pharmacokinetics is the mathematical study of the time-course of drug absorption, distribution, metabolism and excretion. One of the simplest parameters to consider when discussing the pharmacokinetics of any drug is the biological *half-life* of a drug ($t_{1/2}$), which is the time taken for the plasma drug concentration to fall by half after administration. A more accurate method of assessing the efficiency of drug elimination is the estimation of drug clearance from the circulation. For example, after intravenous administration, the $t_{1/2}$ of the drug may be calculated from its plasma concentration–time curve. This simplistic model is based on a single compartment model that states that, following intravenous administration, the distribution of a drug assumes a uniform concentration throughout all compartments (intracellular and extracellular); the elimination by both metabolism and renal excretion is also assumed to be directly proportional to the drug concentration. If this is the case, the volume of distribution may be calculated as:

$$V_d = \text{dose}/C_0$$

where C_0 is the estimated (plasma) concentration at the time of injection.

The apparent volume of distribution is defined as the volume of fluid required to contain the total amount of drug in the body at the same concentration as that present in plasma. Drugs in general may be confined to the plasma compartment because they are either too large to cross the capillary wall or are highly protein-bound (e.g. heparin and warfarin, respectively). Drugs may also be distributed only to the extracellular compartment because they have low lipid solubility (e.g. gentamicin) or distributed throughout all aqueous compartments if they are lipid-soluble. When both the volume of distribution and renal clearance of a drug are known, the $t_{1/2}$ may be estimated. However, when considering a single compartment model, no account is taken of distribution into tissue compartments and metabolism within tissue compartments. When repeated injections of the drug are given, the plasma concentration becomes a function of the rate of both elimination and administration, and the plasma concentration will equilibrate when these two parameters are equal. A steady-state plasma concentration is therefore reached, which in practice may be established after an interval of about three or four plasma half-life lives of the drug given. To reach a steady-state concentration more quickly, loading doses of the drug are often given (for example, antibiotics and warfarin) (Fig. 6-1). In clinical practice the $t_{1/2}$ is important because it will determine the frequency of administration of a drug. If continued intravenous boluses are given, there are frequently large peaks and troughs in drug concentration, which can lead to a greater incidence of toxic side-effects.

Bioavailability describes the amount of oral dose that reaches the systemic circulation and becomes available to the site of drug action. However, this blanket term is not sufficiently precise because rapidly absorbed drugs will reach a much higher plasma concentration than those absorbed slowly and, similarly, rapid elimination would also theoretically lead to low bioavailability. Bioavailability of a drug is measured as the area under the curve of log plasma concentration against time for both intravenous and oral administration, although the reliability of quantitative drug assessment may be variable for several reasons. For instance, the degree of bioavailability may be altered

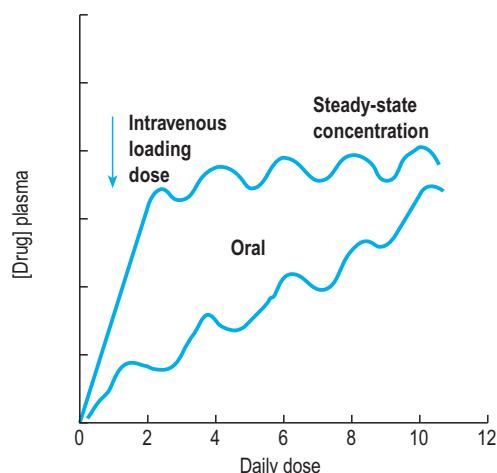


FIGURE 6-1 Plasma concentration of drugs after oral and intravenous administration.

by incomplete absorption of the drug or destruction of the drug by *first-pass metabolism* before the drug reaches the plasma compartment, irrespective of the rate of absorption from the gastrointestinal tract. Drugs instilled into the eye are absorbed from the nasal and nasopharyngeal mucosae directly into the systemic circulation. As such, they escape first-pass metabolism and have a high bioavailability. Thus, topically administered agents can give rise to quite marked systemic effects (see below).

Drug kinetics can be described as first-order (linear) or zero-order (non-linear, saturation) kinetics (Fig. 6-2). First-order kinetics describes a process where rate is proportional to the amount of drug present and can be defined by linear differential equations. Zero-order kinetics occurs when drug dynamics show *saturation* at high drug concentrations. Saturation may occur, for example, when the capacity of drug-metabolizing liver enzymes is surpassed, leading to unmetabolized drug in the circulation for longer periods. The duration of action of a drug that exhibits saturation kinetics is more dependent on the administering dose than in drugs that exhibit first-order kinetics. Also, there is no direct relationship between drug dose and steady-state plasma concentration in zero-order kinetics, which may explain sudden unexpected drug toxicity in a number of clinical settings. For this reason, close drug monitoring is required (e.g. phenytoin).

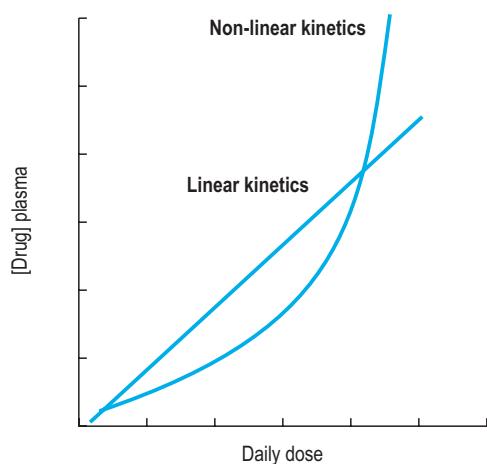


FIGURE 6-2 First-order and zero-order pharmacokinetics.

DRUG ABSORPTION

For a drug to reach the site at which it produces its effect, it must first be absorbed from its site of administration. In general, drug penetration of cell membranes increases with lipid solubility. Drugs can cross cell membranes by diffusing directly through lipid, by diffusion through aqueous pores that traverse the lipid, by utilizing carrier molecules, or by pinocytosis by the cell.

The rate of passage (diffusion) through a cell membrane can be predicted by Fick's law

Non-polar substances dissolve freely in lipid and therefore penetrate the cell by diffusion. The lipid solubility, degree of ionization and molecular size of the drug will determine its diffusion coefficient. The rate is determined by Fick's law, which states that the rate at which drugs cross a biological membrane is directly proportional to the concentration gradient across the membrane and the diffusion coefficient, and inversely proportional to the cell membrane thickness (see below):

$$\text{Rate of diffusion} = KA(x_1 - x_2)/D$$

where K is the diffusion constant, A is the diffusion area, $x_1 - x_2$ is the concentration difference between plasma and intracellular compartments, and D is the thickness of the membrane.

Active transport

As for active transport of ions (see Ch. 4, p. 161), active transport of large polar drugs requires energy-dependent carrier-mediated mechanisms. These transport systems may be disrupted by inhibiting enzyme-dependent carriers or by blocking the carrier mechanism with structurally similar drugs (analogues). Facilitated transport is carrier-mediated transport that does not require energy because it does not proceed against a concentration gradient, for example glucose transport into erythrocytes.

DRUG ABSORPTION IS DEPENDENT ON A DRUG'S LIPID SOLUBILITY

Drug properties

The absorption of a drug depends on its lipid solubility and inversely on its polarity or degree of ionization. An important factor in the degree of penetration of a drug through membranes is that many drugs are weak acids or weak bases. The more the drug is in its un-ionized form, the more likely it is to be lipid-soluble and transferred by passive diffusion through the membrane. For a weak acid or base the pK_a value will determine the degree of ionization, as described by the Henderson–Hasselbalch equation.

For a weak acid the ionizing reaction is:

$$\text{pH} = \text{p}K_a + \log\{\text{[A}^-]/[\text{HA}]\}$$

and for a weak base it is:

$$\text{pH} = \text{p}K_a + \log\{\text{[B]}/[\text{BH}^+]\}$$

The pK_a is a measure of the relative strength (degree of ionization) of a weak acid or base (the pK_a of a drug is that point at which the compound is 50% ionized). The lipid solubility of the uncharged species also depends on the chemical nature of the drug. For example, although streptomycin and the related aminoglycosides are uncharged, the high percentage of hydrogen-bonding groups within these molecules renders them hydrophilic.

The molecular shape, as well as the charge distribution, of the drug molecule determines which membrane pores it may traverse. Small polar molecules, such as urea, readily traverse small aqueous pores in the membrane, thus accounting for the high

permeability of cell membranes to these substances. Most drugs, however, are too large to pass through these pores.

The rate of drug absorption varies with the route of administration

The main routes of administration (besides intravenous) are oral, sublingual, rectal, topical (e.g. skin, conjunctival fornix), subcutaneous and intramuscular.

Absorption of orally administered drugs is affected by gastric pH, rate of emptying of gastric contents, presence of food, and surface area of absorptive mucosa (in disorders such as Crohn's disease the absorptive surface area may be reduced). It is important to consider drug interactions during multiple drug therapy and their effect on drug absorption. For example, in migraine, gastric emptying is delayed, reducing the absorption of analgesics such as aspirin and paracetamol. This may be overcome with the adjunctive use of parenteral metoclopramide, which increases the rate of gastric emptying. The presence of food is generally unimportant, except in the case of tetracyclines (used to treat certain forms of external eye disease commonly associated with acne rosacea), which form insoluble salts with magnesium and calcium. Some drugs will be inactivated within the gut lumen (e.g. benzylpenicillin and insulin). Most mal-absorption syndromes do not affect drug absorption, but in other disorders, such as congestive cardiac failure, drug absorption may be impaired because of the secondary gastrointestinal mucosal oedema. Factors affecting bioavailability are shown in [Box 6-1](#).

DRUG DISTRIBUTION

Once a drug is absorbed, it has the potential to penetrate most compartments of the body so the

BOX 6-1 FACTORS ALTERING ABSORPTION AND BIOAVAILABILITY FROM GUT

- Gut motility
- Intestinal pH, mucus, bile salts
- Enterohepatic circulation
- Exercise
- Reduced absorptive area
- Reduced intestinal blood flow
- Intestinal microflora that may metabolize some drugs

distribution of the drug depends largely on the route of administration. Intravenous and intramuscular administration of a drug result in high drug availability. Buccal (sublingual) absorption of a drug is used to reduce the extent of first-pass metabolism by the liver (as with topically applied eye drops), which invariably occurs with orally administered drugs that reach the liver via the portal circulation. The distribution of the drug and its ability to penetrate cells is also dependent on its physicochemical properties and thus the extent of binding to tissue proteins or cell membrane receptors ([Box 6-2](#)).

Once the drug has reached the systemic circulation, it may become bound to circulating proteins, commonly *albumin* or α_1 -acid glycoproteins (for basic drugs). Protein-bound drugs are restricted in their distribution into tissues, which reduces the availability of the free drug for pharmacological effect. This, in turn, depends on the affinity of the protein for the drug. High levels of protein binding may occur with acidic drugs that are bound to albumin. If a drug is less than 90% bound to plasma proteins, changes in the plasma protein concentration make little difference to the overall amount of unbound drug in the circulation. In cases of drugs with a high binding affinity for protein, a decrease in the steady-state total concentration of the drug, and as a consequence a comparative increase in the clearance of the increased amount of free drug, would occur if for any reason protein binding was impaired. For instance, impaired plasma protein binding in the case of phenytoin results in peaks of unbound active drug in the plasma.

Basic drugs are bound in varying degrees to α_1 -acid glycoprotein, a protein that increases in concentration in certain pathological conditions such as acute inflammation. Under such conditions, the binding of basic drugs (e.g. propranolol) may be increased, thus reducing their effect.

BOX 6-2 FACTORS AFFECTING DRUG DISTRIBUTION

- Physicochemical properties of drug
- Binding to plasma proteins
- Binding to tissue proteins
- Relative blood flow to different tissues

Systemic factors that alter protein binding include hypoalbuminaemia (plasma concentration of albumin less than 25 g/L), renal failure, competition by other highly protein-bound drugs, and changes occurring during the last trimester of pregnancy, such as the diluting effect of the increased plasma volume. In general, competition for binding by other drugs is the major factor affecting distribution because adequate compensatory mechanisms can be initiated to counteract the other causes. The distribution of a drug, as mentioned above, may also be regulated by the binding of a drug to tissue proteins, a process regulated by the abundance of binding sites, affinity constants and the binding of a drug to its receptor. This in turn may give rise to a desired or undesired effect, although receptor numbers are unlikely to be high enough to alter the distribution of the drug appreciably.

In the eye, both the blood-retinal barrier and the blood-aqueous barrier (see Ch. 1, p. 30) limit the distribution of drugs. Tight junctions between the retinal pigment epithelium (RPE) and endothelium of the retinal vessel endothelium give rise to a relatively impermeable barrier to water solutes and larger molecules. Under normal conditions only lipid-soluble drugs will move between the blood and retina. Similarly, the apical membranes of the non-pigmented ciliary body epithelium and the capillary endothelium of the iris are bound by tight junctions, raising a barrier to all but lipid-soluble drugs (see Ch. 1, p. 28).

DRUGS ARE METABOLIZED TO FACILITATE CLEARANCE

The metabolism of most drugs occurs almost entirely in the liver, enzymatically altering the drug to increase its water solubility in preparation for excretion, and simultaneously making the compound metabolically and pharmacologically active or inactive. Metabolism can affect the drug in various ways. The first is activation of the parent drug, which may itself be inactive (known as a *prodrug*). The drug may be metabolized to form active metabolites, as for example in the case of diamorphine and diazepam. However, metabolism of a drug can also produce toxic metabolites that may persist in the circulation for longer than the parent molecule and thus restrict the continued use of such drugs (e.g. lidocaine). In general,

most drug metabolism modifies the drug so that it can then be excreted, usually in the urine but sometimes in bile.

Drug metabolism takes place in two stages: phase I (oxidation) and phase II (conjugation). Phase I reactions are carried out by a heterogeneous group of microsomal enzymes called cytochrome P₄₅₀, of which various forms exist (Box 6-3).

This enzyme system exists in abundance in the liver but is also found in some peripheral organs, including the eye. It is important to note that the activity of these enzymes can be induced by other drugs (e.g. phenytoin and carbamazepine), which accounts for many well-recognized drug interactions. Conjugation reactions appear not to be affected by enzyme-inducing drugs to the same extent as oxidative metabolism. There are also other oxidative enzymes that are not part of the cytochrome P₄₅₀ system but which are involved in drug metabolism; these include xanthine oxidase (e.g. purine metabolism), alcohol dehydrogenase and monoamine oxidase (e.g. catecholamine metabolism). Many drugs also affect the function of microsomal enzyme systems (Box 6-4).

The metabolism of a drug is dependent on several factors. Oxidative metabolism is affected by age. Premature babies metabolize poorly and, similarly in the elderly, oxidative drug metabolism is reduced because of reduced liver size. Smoking may induce certain liver enzymes, necessitating an increased dose of drug for a required effect. Alcohol, on the other hand,

BOX 6-3 DRUG-METABOLIZING SYSTEMS

PHASE I METABOLISM: OXIDATION

Cytochrome P₄₅₀ (microsomal)

- aromatic hydroxylation
- aliphatic hydroxylation
- N-deamination
- N-dealkylation
- S-oxidation
- desulphuration

PHASE II METABOLISM: CONJUGATION

Conjugation occurs with:

- glucuronic acid
- glycine
- glutamine
- sulphate
- acetate

BOX 6-4 DRUGS ACTING AS MICROSOMAL ENZYME MANIPULATORS

ENZYME INDUCERS

- barbiturates
- phenytoin
- phenothiazines
- rifampicin
- griseofulvin
- nicotine

ENZYME INHIBITORS

- isoniazid
- chloramphenicol
- metronidazole
- warfarin
- carbon monoxide

inhibits drug metabolism, particularly during and after binge drinking. Both severe liver disease and poor nutrition may markedly impair drug metabolism.

METABOLIZED DRUGS ARE EXCRETED IN URINE AND BILE

Renal excretion

Drugs differ greatly in their excretion via the kidney. Some drugs are cleared in a single transit through the kidney, while others are poorly cleared. This difference is dependent on the kidney's ability to handle the drug and on physicochemical properties of the drug. Certain drugs may be filtered through the glomerulus (depending on molecular weight), others are actively secreted by the tubules, and still others passively diffuse across the tubular epithelia (reabsorption).

Glomerular filtration. Glomerular excretion of a drug is only possible when drugs are not bound to plasma proteins, and the drug is of a molecular size that can be filtered freely, irrespective of charge (less than 20 000 Da). The clearance of the drug is therefore related to the unbound fraction of the drug and is dependent on the glomerular filtration rate. Glomerular filtration at most removes only about 20% of drug reaching the kidney; the remaining drug passes to the capillaries lining the tubules. Most drugs are presented to the kidney in a carrier form and thus their clearance is slow. Carrier-mediated transport can increase the clearance of the drug even if it is highly bound.

Benzylpenicillin is 80% bound and cleared very slowly by glomerular filtration but is almost completely removed by tubular secretion.

Secretion. Drugs may be actively secreted by the tubules into the glomerular filtrate. Different secretory systems, which are relatively non-selective carrier systems, exist for acidic, basic and neutral drug transport into the tubular lumen. Competition for active sites occurs, so that the secretion of drugs can be blocked by other drugs, for example secretion of penicillins is blocked by probenecid, thus decreasing the excretion of the drug.

Reabsorption. If the tubules were freely permeable to drugs, the drug concentration in the filtrate would be similar to that in plasma. Drug reabsorption occurs mainly as a result of the enormous reabsorption of water achieved by the nephron. This builds up a concentration gradient that drives the drug back into the plasma. Thus drugs that are highly lipid-soluble are excreted slowly and the reabsorption of drugs, especially those that are weak acids or bases, depends on the drug being in its un-ionized form. Therefore, altering the pH of the urine will increase the elimination of the drug, so that acidic drugs are eliminated more quickly in alkaline urine. This manipulation of urine pH is utilized clinically for the treatment of aspirin overdoses, where forced alkaline diuresis is an effective way of increasing the excretion of the acidic drug. Measurement of glomerular filtration can be achieved with the use of agents that are completely filtered and neither secreted nor reabsorbed, for example inulin. Conversely, the clearance of a drug that is completely secreted in one transit through the kidney will correspond to the renal plasma flow, for example *p*-aminohippuric acid.

Biliary excretion

Liver cells also possess transport systems similar to those in the renal tubules, which can transfer drug metabolites from blood to bile. Conjugated drugs (particularly with glucuronate) are concentrated in the bile and delivered to the intestine, where the conjugate may be hydrolysed, releasing the active drug (Fig. 6-3). The drug may then be reabsorbed and its duration of action prolonged (enterohepatic circulation).

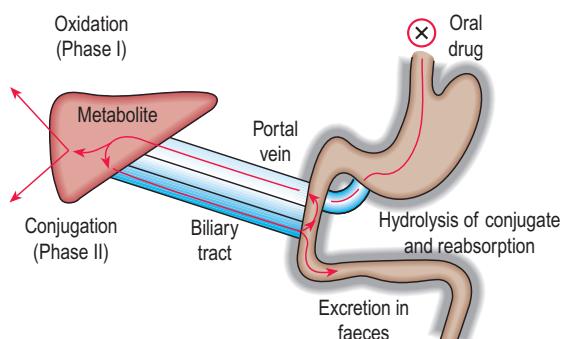


FIGURE 6-3 Drug metabolism: enterohepatic circulation.

This is particularly important for digoxin, which is excreted in the bile in an unconjugated form, and for morphine, which is transported as a glucuronide. Some drugs, for example rifampicin, are excreted into the bile and will be excreted unchanged in the faeces.

Pharmacodynamics: drug handling by the body

Pharmacodynamics considers the effects of a drug and the relationship between drug concentration and response. The drug effect is usually initiated by its binding to a cellular membrane receptor, which is specific for the drug, as is the case with autonomic nervous system neurotransmitters, or by non-specific mechanisms, where specific cell membrane receptors do not exist but drug action is dependent solely on its physical properties (i.e. lipid solubility), or by its ability to inhibit specific biochemical enzymes. The effects of enzyme inhibition may be direct, for example by blocking sodium/potassium ATPase pumps or closing ion channels, or indirect, for example by acting on calcium channels. Some drugs act on intracytoplasmic receptors or cell nucleus receptors. The variety of drug actions is presented in Box 6-5.

Additional content available at <https://expertconsult.inkling.com/>

Drug–receptor interactions

Drugs bind to target molecules on the cell, which then initiate their pharmacological effect. Receptors are proteins that, in general, are situated on the cell surface

BOX 6-5 RECEPTORS

Receptors are unique cell surface proteins capable of binding specific associated substances (ligands). Receptors may be divided into subtypes, depending on the type of agonist or antagonist associated with them. Often receptors can be downregulated or upregulated in different disease states or with chronic drug usage.

A ligand is a specific compound (drug or natural substance) that binds to a receptor.

Agonists are substances that, when bound to a receptor, produce a response that may result in stimulation or inhibition of cell function.

Antagonists are substances that prevent receptor activation.

A partial agonist is a ligand that possesses both antagonist and agonist properties. As such, its maximal effect is less than that of a pure agonist. However, when occupying a receptor it prevents the actions of other agonists, which are therefore less efficacious.

and are able to bind ligands (e.g. neurotransmitters and hormones) (see Box 6-5). The recognition of a ligand by a receptor is analogous to antibody–antigen binding, that is the lock and key principle (see Ch. 7, p. 397). The molecular mechanisms involved in this receptor–effector pathway are known as *transduction* mechanisms, where the receptor is linked either directly or indirectly to the effector system altering cell function. Several forms of receptor–effector linkage are recognized, and include:

- direct regulation of membrane permeability to ions
- regulation of cell function via an intracellular second messenger
- regulation of cell function by regulating DNA transcription and protein synthesis.

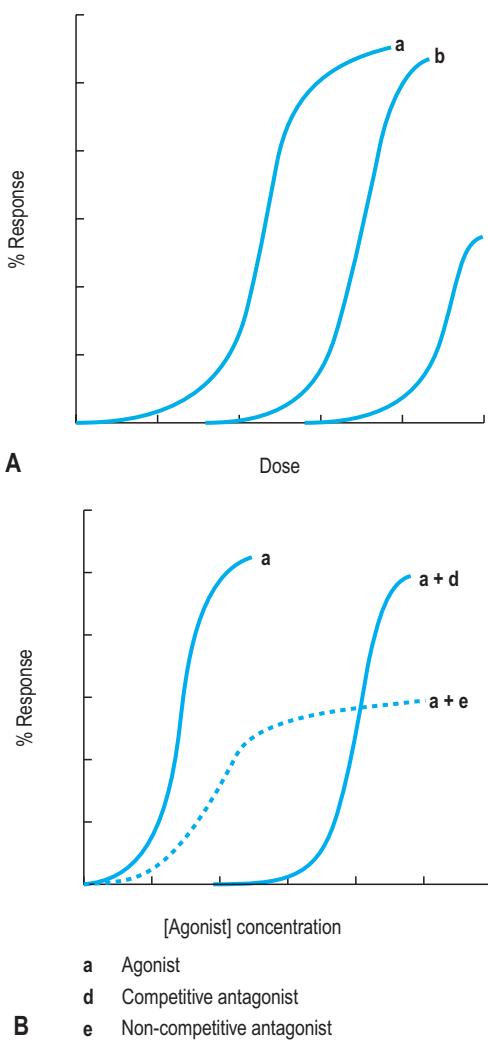
ION CHANNELS

Receptors can be linked directly with ion channels, which function only when the receptor is occupied by an agonist. This is the fastest type of receptor response, as, for example, when a neurotransmitter acts on a nerve ending. The excitatory neurotransmitters acetylcholine and glutamate cause a direct increase in both sodium and potassium permeability, which results in depolarization of the cell (see Ch. 5, p. 287). An equilibrium between open and closed ion channels exists and random fluctuations in conductance occur when

Drugs and receptors

A drug that acts on a receptor may act as an *agonist* or *antagonist*, depending on the response that is elicited. In eFigure 6-1A, drugs a and b are both agonists, but drug b is less potent. Drug c, on the other hand, acts as a partial agonist. Antagonists can be either competitive or non-competitive. If the antagonist is displaced by increasing concentrations of the drug (agonist), then competitive inhibition is present. Non-competitive antagonism describes the situation where the antagonist blocks the action of the agonist without competing with the receptor, which may not be overcome by increasing the concentration of the agonist, so shifting the curve to the right and depressing the maximal response (eFig. 6-1B).

Drugs often give a graded dose-response curve, where increasing the drug concentration will increase the drug effect. This graded response is seen with drugs that are not permanently bound to the receptor. Thus the *efficacy* of a drug is defined as the maximal response it can give, whereas *potency* describes the amount of drug required to give the desired response. Thus some drugs may be efficacious but not potent, requiring large doses to give an effect. However, if the drug is irreversibly bound to the receptor, its effect will continue well after the elimination of the drug from the bloodstream. Alternatively, the efficacy of a drug may diminish with time, an effect known as *tolerance*, which is thought to be the result of downregulation of specific drug receptors. Some drugs also produce active metabolites that continue to give a pharmacological effect well beyond the half-life of the parent drug. All these effects may complicate the study of pharmacokinetics.



eFIGURE 6-1 (A) Potency of receptor stimulation by agonists and partial agonists. (B) The effects of agonist action by competitive and non-competitive antagonists.

the ion channels are opened (or closed) after receptor stimulation. The duration of this response can be measured and is referred to as the *mean channel lifetime*.

SECOND MESSENGERS

Receptor binding on extracellular receptors alters intracellular functions by activating a secondary messenger, for example the activation of the enzyme *adenyl cyclase* and calcium ion influx. Activation of these secondary messengers regulates various intracellular activities. In many cases they generate protein kinase activation and phosphorylation of membrane proteins (see Ch. 4, p. 235). The consequence of any change in protein conformation of the cell membrane may lead to opening of ion channels (e.g. sodium/potassium or calcium channels). Adenyl cyclase may also be activated by G proteins, which are discussed below.

Cyclic adenosine monophosphate (cAMP)

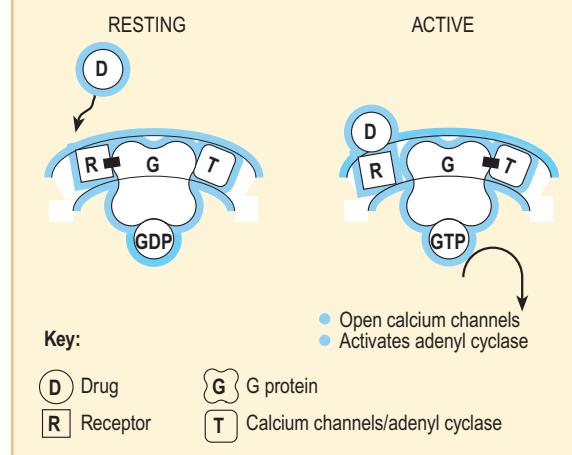
Cyclic AMP is a nucleotide synthesized within the cell from adenosine triphosphate (ATP) by the enzyme *adenyl cyclase*, and is inactivated enzymatically to 5'AMP by hydroxylation with a group of enzymes called *phosphodiesterases*. The following components are required to generate a secondary messenger: a receptor, which faces outwards from the cell; a regulatory protein (G protein), which faces inward towards the cytoplasm; adenyl cyclase; and a cAMP-dependent protein kinase. Inhibition of the secondary messenger activation can be induced with cholera toxin, which binds specifically to the G protein in the intestinal mucosa and thus prevents hydrolysis of another membrane nucleotide, guanine triphosphate (GTP), and adenyl cyclase (Box 6-6).

CALCIUM IS A MAJOR MEDIATOR OF CELLULAR ACTIVITY

Virtually all the calcium in the body is in the skeleton as hydroxyapatite. Intracellular calcium only constitutes 1% of total body calcium. The plasma concentration of calcium is 2.5 mmol/L; 50% is in its ionized form and 50% is bound to proteins or complexed with anions. A rise in the intracellular free calcium concentration can occur as a response to hormones and transmitters, by a net influx of calcium ions into

BOX 6-6 GPROTEINS REGULATE SECOND MESSENGER ACTIVITY

Gproteins are so called because of their affiliation with the guanine nucleotides GTP and GDP. They consist of three subunits, which catalyse GTP conversion to GDP. In the resting (empty receptor) state, the Gprotein–GDP complex is associated with the receptor. The presumed conformational change in the cell membrane when the receptor is occupied acts to increase the affinity of the neighbouring Gprotein for GTP and to promote the binding of the Gprotein–GTP complex to the effector site. This complex can activate ion channels, adenyl cyclase and other secondary messengers, as shown in the figure below.



the cell. It may also occur as a result of a release of sequestered calcium without a net influx into the cell. The intracellular calcium concentration is 10^{-7} mol/L, most of which is protein bound, and small changes in free calcium concentration may affect many intracellular processes. Intracellular calcium is normally regulated by an ATP-active transport channel. Accompanying the increase in intracellular calcium level, there is also an increase in the rate of degradation of minor membrane phospholipids (phosphatidylinositol) by phospholipase C, which in turn alters the membrane permeability and control of membrane phosphorylation, either directly, via its effect on protein kinases, or indirectly, through activation of adenyl cyclase. At the same time a phospholipid flip-flop mechanism occurs within the cell membrane,

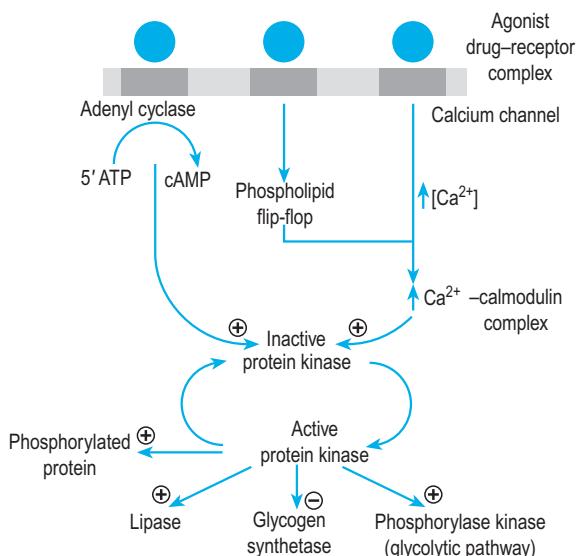


FIGURE 6-4 Activation of membrane-associated enzymes by calcium–calmodulin secondary messengers.

where methylation of phospholipids converting phosphatidylethanolamine to phosphatidylcholine takes place. This further increases calcium permeability, and secondarily regulates adenyl cyclase activation. Intracellular effects of calcium are controlled by an intracellular acidic protein, calmodulin. The calcium–calmodulin complex can thus activate many enzyme systems, including protein kinases, adenyl cyclase, phosphodiesterases and calcium-dependent ATPase (Fig. 6-4). The calcium–calmodulin complex is inactivated via the binding of trifluoperazine (an anti-psychotic agent), which can be used to study the mechanism of action of certain therapeutic agents.

REGULATION OF PROTEIN SYNTHESIS

Steroid hormones, because they are lipophilic, can diffuse across the cell membrane and bind to cytoplasmic receptors and nuclear chromatin. Certain regions of the DNA sequence show a high affinity for steroid–receptor complexes, and binding of these complexes generates an increase in RNA polymerase activity and generation of messenger RNA (mRNA) and thus production of proteins (see Ch. 3, p. 133). One steroid may result in the production of several different species of mRNA within each cell, which may explain the great diversity of steroid actions.

Ligand–receptor affinity determines selectivity

The affinity of a ligand for its receptor is measured by the amount of ligand required to achieve half-maximal binding (EC_{50}). The binding force of the receptor–ligand complex can also be measured by the length of time taken for dissociation of the complex to occur. Low-affinity agonists include those required to potentiate a rapid response (e.g. neurotransmitters), and therefore concentrations of the ligand close to the receptor during stimulation must be high. The selectivity of a ligand for receptors is a ratio of the EC_{50} for the receptors being compared. If the ligand (or drug) is more selective for receptor A than for receptor B, it will achieve its clinical effect by stimulation of receptor A at lower doses, but will still stimulate receptor B if sufficient drug is given. Therefore, clinically, it is important to establish the EC_{50} ratio of a given drug; ratios lower than 50 are considered unsafe for clinical use if stimulation of other receptors is to be avoided.

Genetic control of drug handling influences response

Defining the genetic make-up within populations or, more pertinently, the individual has assisted in understanding responses to drugs. The hope is that with such understanding we may not only increase our knowledge of disease pathogenesis but also develop tailored therapies for the individual, whilst reducing adverse effects.

There are historical examples of clear distinctions in the individual's capability to metabolize drugs. N-acetylation may be either fast or slow, depending on the amount of enzyme present, which is controlled by a single recessive gene associated with low hepatic acetyltransferase activity (e.g. in isoniazid metabolism). Patients with low acetyltransferase activity are known as *slow acetylators*. Another genetic variation in the rate of drug metabolism is seen with suxamethonium (a depolarizing neuromuscular blocker used in general anaesthesia). About 1 in 3000 individuals fails to inactivate suxamethonium by hydrolysis (pseudocholinesterase), which is the result of a recessive gene that gives rise, in homozygotes, to an abnormal cholinesterase with a much lower substrate affinity. Patients who have a hereditary erythrocyte glucose-6-phosphate dehydrogenase enzyme deficiency may develop a haemolytic anaemia when treated with a number of

drugs, including chloroquine, vitamin K, acetylsalicylic acid (aspirin) and probenecid.

P450 gene. The drug-metabolizing cytochrome P450 enzyme genes have been identified and cloned to include a large family of mono-oxygenases. Genes encoding P450 enzymes are polymorphic and within three families. As a result there are in broadly four functional outcomes: *fast* metabolizers who inherit multiple gene copies; *normal* metabolizers who have two normal alleles; *intermediate* metabolizers who have one deficient allele; and *poor* metabolizers who lack the functional enzyme.

The genes encoding families of enzymes are called *cyp* and are given numbers associated with a specific group of enzymes within the gene family, subfamily and then specific gene itself: e.g. CYP27A1 relates to group 27, subfamily A and gene 1.

In the eye *CYP1B1* is a gene that encodes for an enzyme localized to the endoplasmic reticulum that is involved in metabolizing aromatic hydrocarbons and steroids. In addition to metabolism, within the eye mutations are linked with congenital glaucoma as well as rare but significant retinal dystrophies such as Best crystalline dystrophy. The aryl hydrocarbons have implications in ageing and cell dysfunction secondary to smoking and cataract formation or age-related degeneration (see Ch. 9, p. 504) (Box 6-7).

BOX 6-7 GENETIC CONTROL OF IMMUNOSUPPRESSIVES DICTATES DRUGS RESPONSE

Azathioprine is a commonly used steroid-sparing immunosuppressant for inflammatory disorders, including for the eye in thyroid eye disease and uveitis. It is a purine analogue, whose active metabolite component, 6-mercaptopurine's conversion to cytotoxic 6-thioguanine analogues inhibits proliferation of cells. Most important is that it carries a significant potential for adverse effects. These have been reduced with improved understanding of pharmacogenetics. 6-mercaptopurine is metabolized via thiopurine methyltransferase (TPMT). Individuals (up to 1:1000 patients) who inherit two non-functional alleles for the polymorphic *TPMT* gene will have dramatic life-threatening myelosuppression. Importantly, up to 15% of the population are heterozygotes and will have increased incidence of myelosuppression. Genetic testing is now available as well as phenotyping by measuring TPMT activity in red blood cells.

Ocular pharmacology: drug handling by cells and tissues of the eye

This section describes the pharmacokinetics, pharmacodynamics and modes of drug delivery (excluding systemic administration) that are used to treat ocular surface and intraocular conditions.

MECHANISMS OF OCULAR DRUG ABSORPTION

There are several methods of administering ocular medications, including extraocular routes (topical) via either conjunctival/episcleral absorption (non-corneal) or transcorneal absorption, and direct intraocular administration of drugs. The non-corneal route of absorption may be significant for drugs that do not penetrate the cornea well. Corneal absorption still represents the major route of absorption for most ocular medication.

FACTORS INFLUENCING DELIVERY OF DRUGS TO THE EYE

Drugs can be administered in many different topical forms, including solutions, gels and ointments. The efficacy of treatment is usually dependent on intraocular penetration, which in turn is dependent on the permeability of the drug across the cornea, and the anatomical and physiological influences of the local environment, including lacrimation, tear drainage and the composition of the precorneal tear film.

Routes of administration

Conjunctiva. Topical administration into the inferior fornix of the conjunctiva is by far the most common route of ocular drug delivery. Both lacrimation and blinking profoundly influence the residence time of fluid in the fornix. Therefore, the efficacy of such delivery systems depends on the anatomy and physiology of the lids, the precorneal tear film, and the health of the conjunctiva, cornea and lacrimal system.

The conjunctival sac has a capacity of approximately 15–30 µL (dependent on blinking) and the natural tear film volume is 7–8 µL. The tears turn over at approximately 16% per minute during a normal blink rate of 15–20 blinks per minute. Most solution applicators deliver between 50 and 100 µL per drop, so a substantial amount of drug will be lost through overspill on administration. The turnover of tears is

also highly dependent on environmental conditions, particularly temperature and humidity. The epithelium of the conjunctiva is continuous with that of the cornea and epidermis of the lids (see Ch. 1, p. 85) and contains goblet cells, which produce mucus and are integral to the stability of the tear film (see Ch. 4, p. 198). Drug absorption through the conjunctiva therefore requires transport firstly through the epithelium. In the subconjunctival stroma, which is a highly vascular conjunctiva owing to the rich superficial venous plexus and lid margin vessels, drugs may be absorbed in significant concentrations into the circulation. Also, after administration into the inferior fornix, drugs drain directly through the nasolacrimal duct into the nose, where measurable systemic absorption of drugs via the nasal and nasopharyngeal mucosa occurs. Restricting the entry of a topically applied ophthalmic dose into the nasal cavity by nasolacrimal occlusion for 5 min, or by making appropriate alterations to the vehicle (i.e. from solution to ointment) increases the residence time of the drug in the fornix, and increases ocular absorption.

Precorneal tear film and cornea

Tears are considered to act as a buffering system for many substances. The pH of normal tears varies between 6.5 and 7.6, while many drug delivery systems are often formulated at pH of less than 7; the return to physiological pH after drug instillation is, however, more likely to be a function of increased tear turnover than the result of a buffering effect. The precorneal tear film is composed of an outer lipid layer (mixed lipids), a middle aqueous layer (including proteins) and a deeper mucin layer (glycoprotein) (see Ch. 4, p. 200). The mucin layer contributes to the stability of the tear film, as well as promoting adherence of the tears to the lipophilic corneal and conjunctival epithelium. Any alteration in the components of the tear film will result in instability of the tear film and a reduced conjunctival residence time of the drug. At the same time alteration in the pH of the tear film may affect the ionization of the drug and thus its diffusion capacity. In spite of the extensive losses to the exterior and to systemic absorption, topical (conjunctival) administration of drugs achieves acceptable intraocular levels, mainly because of the very high concentrations that are administered.

The pH of the tear fluid is important in drug formulation because of the physiological homeostatic mechanisms. Drug penetration may be enhanced by changing the degree of drug ionization and enhancing the product stabilization over a range of pH changes. The epithelium of the cornea represents the most important barrier to intraocular transport of drugs via this route. First, the stratified cellular epithelium is bound by desmosomes between the lateral borders of the superficial cells. Second, the corneal epithelium is hydrophobic (as are all cell membranes), and so will allow only lipid-soluble drugs to pass through. In addition, Bowman's membrane, an acellular collagenous sheet (10 µm thick) between the basement membrane of the epithelium and the stroma of the cornea, acts as a further barrier to the penetration of drugs. In contrast, the stroma, which accounts for 90% of the corneal substance and its ground substance (glycosaminoglycans and water), permits ionized water-soluble drugs to pass more efficiently than lipid-soluble drugs. Finally, transport across the single-layer endothelium of the cornea is relatively free because it contains gap junctions that permit good penetration of most drugs into the aqueous humour. Many topical eye medications are weak bases, for example tropicamide, cyclopentolate and atropine, and exist in both ionized and un-ionized forms within the pH range of the tear film (pH 7.4). Altering the solution pH of timolol (pK_a 9.2) from 6.2 to 7.5 increases its corneal penetration and systemic absorption. The partition coefficient (ratio of concentrations in the two compartments) may therefore be increased by raising the pH of the water phase, rendering the drug non-ionized and more lipid-soluble. The factors affecting topical drug absorption are summarized in Box 6-8.

BOX 6-8 FACTORS INFLUENCING TOPICAL DRUG ABSORPTION

- Environmental conditions – temperature and humidity
- Volume of drug application
- Drug formulation – pH, preservative, vehicle type
- Blink rate
- Stability of tear film
- Absorption through conjunctival vessels and nasal mucosa
- Corneal epithelium and stroma
- Nasolacrimal drainage of tears

Delivery methods of ocular medication

RESIDENCE IN THE CONJUNCTIVAL SAC

The bioavailability of ocular medication depends on the precorneal fluid dynamics, drug binding to tear proteins, conjunctival drug absorption, systemic drug absorption, resistance to corneal penetration, drug binding to melanin and intraocular drug metabolism. Both the absorption and the efficacy of the drug can be increased by altering the formulation of the drug and/or by changing the local conditions.

To increase the residence time of the drug in the inferior fornix, and thus its delivery to the corneal epithelium, attempts at reducing the instilled volume of drug and increasing the viscosity of the solution have been made. For instance, polymers that increase solution viscosity include polyvinyl alcohol, hydroxypropylcellulose and other cellulose derivatives. However, increasing the viscosity of the delivery solution only produces a modest gain in ocular drug absorption, particularly for lipid-soluble drugs.

The residence time for many drugs is especially reduced by their pH, tonicity and the direct effect of certain drugs on lacrimation, which all affect the residence time of drugs in the lower fornix. For example, formulation at acidic or alkaline pH is irritant to the eye and increases both lacrimation and the blink rate, and clearance of the drug. Attempts to reduce the tonicity of the drug solution by using dilute buffers (e.g. phosphate buffers) to prevent stinging and lacrimation, and therefore increase transit time (reduce clearance), have also been employed. Drugs that have a direct pharmacological action on the lacrimal gland, increasing lacrimation and subsequently altering the precorneal fluid dynamics, include muscarinic agonists. Some drugs are also bound to the tear proteins (albumin, globulins and lysozyme), reducing the concentration of the free drug available for absorption.

The corneal epithelium presents a considerably greater barrier to hydrophilic than to lipophilic drugs (10:1). Corneal epithelial permeability, however, may be increased during ocular inflammation so that some drugs, for example dexamethasone, are more rapidly absorbed across the corneal epithelium into the eye. Preservatives such as benzalkonium chloride have also been shown to enhance the ocular absorption of drugs. Benzalkonium chloride and other cationic

surfactants increase the ocular absorption of drugs by increasing corneal permeability (by compromising corneal integrity), depending on the molecular size and lipophilicity of the drug. Increased absorption can be obtained with pilocarpine, prednisolone and homatropine. For a drug to penetrate optimally, it must be able to exist in both ionized and un-ionized forms. Drugs will be buffered by the precorneal tear film and any alteration in the pH will change the ratio of ionized to un-ionized forms of the drug, dependent on the pK_a of the drug. In general a drug that exists in a purely ionized form will not penetrate the cornea unless the cornea has been damaged. Once absorbed into the eye, drugs may be bound to melanin within the pigment epithelium of the iris and the ciliary body, which may in turn reduce the bioavailability of the drug and also retard its clearance, leading to increased and prolonged drug levels. Similarly, after penetrating into the eye, drugs may be rendered inactive by intraocular metabolism. Enzymes that participate in ocular drug metabolism include those involved in inactivating neurotransmitters, for example monoamine oxidase, catechol O-methyltransferase, esterases, cytochrome P₄₅₀, and other enzymes including ketone transferase, glucuronidase and aldose reductase within the lens (Box 6-9). The majority of enzyme activity is microsomal, although some enzymes, for example esterases, are both cytosolic and extracellular. Within the anterior segment, the corneal endothelium, the non-pigmented cells of the iris, and the ciliary body are metabolically most active, so drugs that are good

BOX 6-9 ENZYMES INVOLVED IN DRUG METABOLISM IN THE EYE

- *Ketone reductase* – this is a cytosolic enzyme dependent on NADPH. It is thought to play a key role in the metabolism of timolol and analogues of propranolol. Found in corneal epithelium, lens, iris and ciliary body
- *Esterases* – important in the activation of ester pro-drugs. Both acetyl- and butyrylcholinesterases are found in rabbits. They are widely distributed throughout the anterior segment
- *Classic phase I and II oxidizing and conjugating enzymes* – cytochrome P₄₅₀ reductase, demethylase, sulphatase and glucuronidase

substrates for these enzymes may suffer substantial degradation during absorption.

DRUG VEHICLES AFFECT DRUG DELIVERY

Several topical drug delivery systems are used in ophthalmology (Box 6-10) and there are a plethora of advances in the pipeline and in early-phase development such as nanoparticles and viral vectors for gene delivery. Nanoparticles are colloidal drug carrier systems in nano- and micro-size range. The advantages are overcoming lipid solubility, improved clinical targeting and depot longer-acting delivery. Similarly there is increasing development of viral delivered genes to replace mutated or loss of gene function in degenerative disease or as a drug depot to release the active component at the tissue site (see Ch. 3, p. 147)

Solutions

Solutions are a common mode of delivery because they cause less blurring of vision than ointments. They are easily administered and achieve high intraocular concentrations if applied regularly. They do, however, possess a short contact time and are quickly washed away at a rate proportional to the volume instilled. Polyvinyl alcohol or methylcellulose added to the solution increases the viscosity and/or lowers the surface tension, and will thus prolong contact time. Biologically active drug compounds that are sparingly soluble in water are often formulated as suspensions. Ophthalmic suspensions, particularly steroids, are thought to be useful delivery systems because it is assumed that the drug particles persist in the conjunctival sac and give rise to a sustained-release effect. Suspensions tend to form precipitates and thus need to be resuspended in the mixing bottle before application.

BOX 6-10 DRUG DELIVERY VEHICLES

- Solutions, colloids, emulsions, suspensions
- Ointments
- Slow-release preparations
- New ophthalmic delivery systems
- Particulates
- Liposomes
- Intravitreal preparations

Semisolids (ointments)

Ointments consist of any one or a combination of hydrocarbons, mineral oils, lanolin and polymers such as polyvinyl alcohol, carbopol and methylcellulose. Drugs applied by this method provide an increase in the duration of action because of reduced dilution, reduced drainage and prolonged corneal contact time. Although these preparations melt at the temperature of the ocular tissue and disperse within the tear film, they are still retained longer than other ophthalmic preparations. They do, however, give rise to blurring of the vision and an increased incidence of contact dermatitis, related commonly to the preservative within the preparation.

Slow-release preparations

The problem of short residence times has been addressed by the development of ingenious vehicle supports. For instance, controlled release of ocular medications can be achieved with conjunctival inserts or with hydrophilic soft contact lenses. Slow-release preparations allow the constant release of drug while minimizing the drainage rate of the drug.

Ocular inserts. Controlled-release delivery systems deliver a bioactive agent to the target site at a controlled concentration over a desired time course. Ocular inserts are flexible, elliptical devices, consisting of three layers. The two outer coats of ethylene vinyl acetate enclose an inner coat of drug/alginate mix. The Ocusert with pilocarpine relies on the solubility properties of pilocarpine-free base, which exhibits both hydrophilic and lipophilic properties. Because the drug is miscible in both aqueous and organic solvent media, it will permeate the hydrophobic controlling membranes by diffusion through the pores. Erodible systems such as Lacrisert® contain drug within carboxymethylcellulose wafers or polyvinyl alcohol disks or rods. They are manufactured principally for the treatment of dry eyes.

Collagen shields. Collagen is thought to be a suitable carrier of drugs. The three polypeptide α -helical chains are held together by cross-linking between proline and hydroxyproline, which account for 30% of the amino acid content of the molecule. Because of the ability to control the amount of cross-linking in

the collagen subunits by exposure to ultraviolet light during manufacture, the time taken to dissolve when placed on the cornea can be altered. Also, collagen acts as an ion exchanger and is semipermeable, facilitating controlled release of drugs. Thus, the collagen bandage shields prolong contact between drug and cornea. Drugs can be incorporated into the collagen matrix, absorbed on to the shield during rehydration, or applied topically over a shield when in the eye. As the shield is erodible, release of the drug occurs gradually into the tear film, maintaining higher concentrations.

Soft contact lens. In this case the polymer of the contact lens is hydrophilic and thus water-soluble drugs are absorbed into the lens. The lens is hydrated once placed on to the cornea and so releases the drug until equilibrium is reached between drug concentration in the contact lens and in the conjunctival sac.

A primary concern with all ocular inserts is comfort, while many other criteria determine their usability (Box 6-11).

Intravitreal inserts. Development of inserts directly applied to the vitreous cavity has gained increasing impetus following the advent of successful trial evidence supporting intravitreal drug administration for macular degeneration and vascular occlusions and CMV viral retinitis (see p. 471). Such inserts include, for example the following:

Ozurdex® is a dexamethasone intravitreal implant inserted directly by injection into the vitreous cavity, using a Novadur® polymer system of poly D,L-lactide-co-glycoside (PLGA) which is biodegradable over months.

Retisert™ is a controlled delivery system of pellets containing the steroid fluocinolone coated in polyvinyl alcohol and silicon laminate which is directly

BOX 6-11 CRITERIA FOR SUCCESSFUL OCULAR INSERTS

- Comfortable and easy handling and insertion
- No expulsion of insert during wear
- No interference with vision
- Negligible interference with oxygen access to cornea
- Reproducibility of kinetics of drug release
- Sterility

inserted to the vitreous and sutured into the sclera for stability.

Ilivien® is a directly injectable-free floating non-biodegradable insert containing the steroid fluocinolone acetonide in a polymide cylindrical tube.

ADVANCED OCULAR DELIVERY SYSTEMS

New ophthalmic delivery system (NODS)

NODS is a method of administering a drug as a single unit volume within a water-soluble preservative-free form. The system is easily administered and may offer a significant improvement in bioavailability over drops. Essentially the device consists of a water-insoluble drug-loaded flange attached to the end of a water-soluble handle by a soluble membrane film. The flange end is placed into the inferior fornix and the membrane rapidly dissolves, releasing the flange, which then hydrates within the inferior fornix and releases the drug.

Particulates

Microspheres and nanoparticles represent promising particulate polymeric drug delivery systems for ophthalmic medications. These systems may avoid the potential disadvantages of other delivery systems, which include discomfort and difficulty of use with inserts, blurring of vision with viscous solutions, and instability of liposomes (see below). They may not represent real particles (capsular wall containing an aqueous or solid core) but are matrix-type structures of lipid base and drug. The particles are formed by polymerization (with ultraviolet light), during or after which the drug may be added. This leads to covalent drug binding to the polymer, so that when the drugs are absorbed into the polymer matrix they form a solid–solution matrix. The binding of the drug depends on its physicochemical properties as well as the nature of the polymer (polybutylcyanoacrylate). Smaller particles are better tolerated by patients than larger ones, and also have increased drug absorption and much slower elimination rates.

Liposomes

Liposomes are vesicles composed of lipid membranes enclosing an aqueous volume. They form spontaneously when a mixture of phospholipids is agitated in an aqueous medium to disperse the two phases, and

are composed of phospholipids, including lecithin, phosphatidylserine and phosphatidylglycerol. They therefore share the properties of the bilayer of an outer cell membrane. The drugs can be trapped in either the lipid or aqueous phase. They provide the possibility of controlled and selective drug delivery and thus increased ocular bioavailability, although liposomes carry lipophilic drugs more readily than hydrophilic ones. The advantage of liposomes is that they are easily prepared, non-irritant, and do not cause any blurring of vision. Altering their surface charge or binding specific ligands to them increases their adherence to cells and subsequent endocytosis of the liposome–drug complex.

Ocular iontophoresis

Iontophoresis is a method of drug delivery that utilizes an electric current to drive a polar drug across a semi-permeable membrane; this may be achieved by either a cathode or an anode, depending on whether the molecule is negatively or positively charged. Applications in clinical ophthalmology have yet to be determined but a possibility may be the iontophoretic application of antibiotics in bacterial keratitis, enhancing tissue penetration of the agent. Corneal iontophoresis of gentamicin and aprofloxacin has been successful in treating experimental pseudomonas keratitis. Trans-scleral iontophoresis allows direct drug penetration into the vitreous but has a major disadvantage of discomfort and may produce small areas of retinal necrosis at sites of application.

INTRACAMERAL AND INTRAVITREAL ADMINISTRATION

Despite the considerable ingenuity applied to the development of topical drug preparations, the treatment of many ocular disorders is hampered by poor penetration into the eye. Systemic drug administration also does not guarantee high intraocular drug levels, in part as a result of the integrity of the blood–retinal and blood–aqueous barriers. For instance, the treatment of bacterial endophthalmitis is often inadequate unless vitrectomy and intravitreal antibiotics are used. The recommended dose of intravitreal antibiotics is based on doses that are not toxic to the rabbit or primate retina, but little is known about dose-response in the human vitreous. Experimentally,

intravenous administration of the newer cephalosporins produces an incremental increase in the vitreous levels in inflamed eyes (but not in normal eyes). In inflammatory conditions, water-soluble antibiotics (penicillins) have a prolonged half-life as the retinal pump mechanism is damaged in such eyes. However, the commonly used aminoglycosides are more rapidly cleared from inflamed eyes, despite low lipid solubility, because they are eliminated through the aqueous circulation. To achieve continual maximal therapeutic concentrations in the vitreous, repeated injections may be required. This may lead to complications of lens injury, haemorrhage, infection and retinal injury, and methods to reduce the toxicity of this form of treatment have included development of liposome-encapsulated drugs, which may be administered directly into the vitreous, or subcutaneously/subconjunctivally, acting as controlled-release formulations. Similar approaches are being sought both in humans and experimental models with other agents, for example ganciclovir for cytomegalovirus retinitis (see eBox 6-1), cyclosporin A for endogenous uveitis and encapsulated anti-fibroblastic drugs (5-fluorouracil) for proliferative vitreoretinopathy.

Intravitreal delivery of drugs has revolutionized care for vascular retinal disorders

Understanding that in neovascular (wet) age-related macular degeneration creating choroidal neovascular membranes or diabetic macular oedema is in part driven by pro-angiogenic growth factor, vascular endothelial growth factor (VEGF) has led to development and implementation of anti-VEGF therapies in clinical practice. There are numerous intravitreal injections of drug available to neutralize VEGF activity (Fig. 6-5). In common, the VEGF inhibitors act to bind to soluble VEGF and block activity by preventing binding to VEGF receptors. VEGF actions are mediated principally via receptors VEGF-R1 and VEGF-R2. *Ranibizumab* is a monoclonal recombinant human Fab VEGF; recombinant human FabV2 is a humanized Fab fragment that binds and neutralizes VEGF and *aptamers* (i.e. *pegaptanib sodium*) are nucleic acid ligands that are specific for given proteins and act as decoys, neutralizing their function. Another decoy mechanism is that of high-affinity VEGF blocker that

eBox 6-1**Treatment of cytomegalovirus (CMV) retinitis**

Ganciclovir was the first agent found to demonstrate therapeutic activity against CMV retinitis (see Ch. 8, p. 473). At least 80% of patients respond to initial treatment with parenteral ganciclovir. Complications following parenteral administration include thrombocytopenia and leucopenia.

Zidovudine (AZT) has no direct antiviral action against CMV but may act by diminishing human immunodeficiency virus (HIV) enhancement of CMV infection and by improving immune function. However, AZT also causes bone marrow suppression, making combined therapy incompatible. Human recombinant granulocyte-macrophage colony-stimulating factor stimulates proliferation, differentiation and chemotaxis of neutrophils and, in combination with anti-CMV and HIV treatment, may prevent neutropenic episodes.

Cidofovir is a DNA polymerase chain inhibitor that can be used at maintenance dose once a week.

Foscarnet may also be used to treat CMV infection, but up to 30% of patients develop renal toxicity. Despite this, it is safer for administration in combination with AZT.

Control of CMV retinitis may occur with intravitreal injections of either ganciclovir or foscarnet. Injections are not directly retinotoxic even though intravitreal levels of these agents are within the toxic range for the drug. Intravitreal injections of liposome-encapsulated drugs reduce the requirement for repeated injection, without any evidence of retinal toxicity.

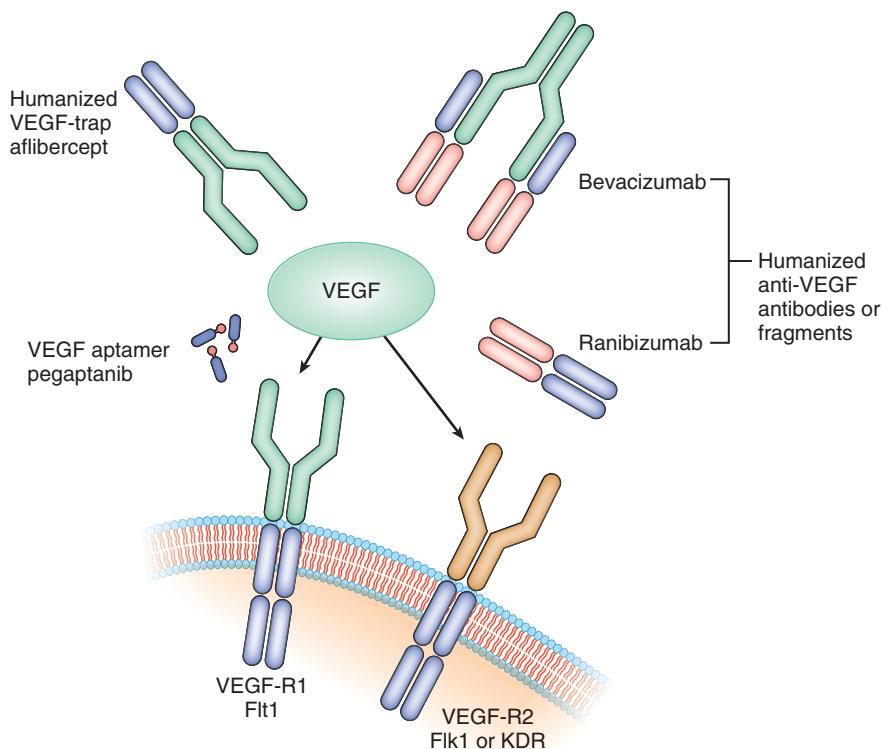


FIGURE 6-5 Intravitreal anti-VEGF therapy. Advent of current biologics to inhibit VEGF activity are shown. They target one of the VEGF family of proteins – VEGF A (there are VEGF A–D). VEGF binds to numerous receptors, including VEGF-R1–R3 and neuropilin receptor. However, the greater receptor affinity for major pro-angiogenic VEGF A actions is via VEGF-R1 and VEGF-R2, as depicted in this schematic.

is a fusion of VEGF receptor 1 to a human immunoglobulin G constant region (afibbercept) (Box 6-12).

DRUGS ADMINISTERED SYSTEMICALLY ALSO PENETRATE THE EYE

The preceding sections focus on the factors that affect the efficacy of topical or direct ophthalmic therapy with minimal systemic side-effects. However, drugs for ocular conditions may be administered systemically to achieve sufficient drug concentration in ocular tissue, although in humans the intraocular drug levels that are reached are largely unknown for most substances.

Commonly used drugs in ophthalmology include the carbonic anhydrase inhibitors (acetazolamide and dichlorphenamide, see below), which are

BOX 6-12 VEGF

VEGF belongs to a platelet-derived growth factor family which includes VEGF A–D.

VEGF A is a product of the *vegfA* gene encoding multiple isoforms identified by their amino acid number (e.g. VEGF₁₆₅).

Alternative splicing may result in two protein families from the same gene, which for the *vegfA* gene, for example, are denoted VEGF₁₆₅ or VEGF_{165b}. The latter is anti-angiogenic and is important for tissue homeostasis.

There are a number of VEGF receptors, which include the major pro-angiogenic receptors VEGF-R1 (Flt1), VEGF-R2 (KDR) mediating via tyrosine kinase's VEGF A effect.

VEGF-R3 (Flt4) mediates lymphangiogenesis through VEGF C and D, while the fourth receptor, neuropilin receptor (NRP1 receptor), which binds VEGF A, is important for cell survival and axonal guidance.

administered orally or intravenously to reduce intraocular pressure. Various animal studies have also demonstrated the ability of systemic antibiotics to reach intraocular infections in concentrations that are bactericidal to certain pathogens. For example, ciprofloxacin penetrates the aqueous humour following oral administration. Similarly, both non-steroidal anti-inflammatory drugs and steroids penetrate the eye when given orally.

Conversely, drugs applied topically may also reach the systemic circulation and affect the contralateral eye. This has been recorded with timolol therapy of chronic open-angled glaucoma with unilateral intraocular pressure rise, which resulted in a significant drop in intraocular pressure in both treated and untreated eyes. In experimental models, a drug effect on the contralateral eye has also been shown with apraclonidine. This phenomenon may occur with a drug possessing a long systemic half-life or unique tissue-binding characteristics within the eye. If supplied in too high a dose or concentration, systemic side-effects may occur, as with 10% phenylephrine drops.

TOPICAL MEDICATIONS AND PRESERVATIVES

Ophthalmic solutions and ointments must be sterile, and a wide variety of preservatives are used for this purpose. Most are toxic to the precorneal tear film and epithelium, impeding epithelial healing and disrupting the tear film. The commonly used preservatives are benzalkonium chloride, thiomersal, chlorbutol and organomercuric compounds. Benzalkonium chloride is a surfactant preservative (cationic preservative) which attains its bactericidal activity by attaching to the bacterial cell wall, increasing permeability and eventually rupturing the cell wall. While these preservatives and other cationic surfactants compromise the corneal integrity, they have also been shown to enhance the ocular absorption of drugs. Benzalkonium chloride is most effective at an alkaline pH (approximately pH 8.0) but is inactivated by the presence of soaps and salts, for example magnesium and calcium. As such, some contact lens solutions also combine ethylenediaminetetra-acetic acid (EDTA; a chelating agent) to overcome this problem. Severe toxicity may result from direct cellular damage or from a hypersensitivity reaction to components of the drug, and give rise to papillary conjunctivitis,

punctate keratitis and corneal oedema. Chlorbutol also reduces oxygen utilization of the cornea (see Ch. 4, p. 203) and may result in epithelial desquamation. Mercurial compounds include phenylmercuric acetate and thiomersal. Hypersensitivity to these compounds is the most dramatic and common complication of preservatives in 10% of patients, and mercurial deposits may develop in corneal tissues. All these preservatives are absorbed to various degrees by soft contact lenses.

Reconstituting the tear film

With increased knowledge of the anatomy and physiology of the precorneal tear film (Ch. 1, p. 89 and Ch. 4, p. 203), tear substitutes have been generated to provide symptomatic relief by artificially reconstituting individual tear film components. Ocular surface disease results from abnormalities in one, but generally more, of the tear film components. Aqueous deficiency is observed classically in keratoconjunctivitis sicca, as occurs in, for example, Sjögren's syndrome. Instillation of artificial tears is the mainstay of treatment in conjunction with reducing drainage by occluding the lacrimal puncta. Mucin deficiency occurs in conditions that affect goblet cell function, for example cicatricial conjunctival disease and hypovitaminosis A, the effect of which is an unstable tear film because the surface tension is reduced and so is insufficient to maintain the aqueous layer. Therefore, areas of non-wetting occur and if left untreated corneal ulceration and scarring can result. Finally, lipid abnormalities are associated with chronic inflammation of the meibomian glands (see Ch. 1, p. 82) and, again, result in an unstable tear film and inadequate wetting of the cornea.

TEAR SUBSTITUTES

Artificial tears or ocular lubricants are generally formulated as solutions consisting of inorganic ions (0.9% NaCl) and polymers to increase wettability and retention time, i.e. they additionally act to replace one of the actions of the mucin component of the tears. Commonly used polymers include polyvinyl alcohol and semisynthetic celluloses. Methylcellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose are still

widely used, although polyvinyl alcohols have additional surfactant properties to further stabilize the tear film for longer periods. Recently, hyaluronic acid has been used, which has much greater retention times than celluloses or polyvinyl alcohols and improves tear film stability. Polyacrylic acid (carbomer) is a gel that is hydrophilic, helping it to form a stable tear film, increasing retention time and thus enabling it to be used less frequently.

Artificial tears are now more commonly available without preservatives. Preservatives affect corneal epithelial stability and thus ability to maintain the pre-corneal tear film.

MUCOLYTICS

Acetylcysteine, which is a derivative of the amino acid L-cysteine, has been used as a mucolytic agent, dissolving the mucus threads that occur in keratoconjunctivitis sicca, but it does not appear to effect corneal wetting so it has to be used in conjunction with other artificial tear preparations.

Ocular drugs and the autonomic nervous system

Parasympathetic and sympathetic divisions of the autonomic nervous system supply both ocular and extraocular tissues vital for normal ocular function (see Ch. 1, p. 64). Agents that influence neurotransmission in the autonomic system are extremely important in the diagnosis and management of many ophthalmic disorders.

THE PARASYMPATHETIC SYSTEM

Acetylcholine is the major neurotransmitter of the parasympathetic system. It is formed enzymatically from choline and acetyl coenzyme A in the nerve endings (Fig. 6-6). Acetylcholine acts on two types of receptors: muscarinic, which are situated at the effector organ (postganglionic), and nicotinic, which are situated at ganglion synapses and also at neuromuscular junctions. In the eye such receptors are found in the motor endplates of extraocular muscles and levator palpebrae superioris, sympathetic and parasympathetic ganglia, iris sphincter, ciliary body and lacrimal glands. The nicotinic–acetylcholine receptor complex

consists of two pairs of polypeptide chains and an additional single polypeptide chain (250 000 Da), providing a hydrophilic channel through which ions can traverse the lipid bilayer. This is known as a *ligand-gated ion channel*. As the acetylcholine binds to the receptor in the synaptic cleft the configuration of the polypeptide chains alters, allowing an influx of sodium and potassium ions down the concentration gradient, thus depolarizing the motor endplate. Cobratoxin, bungarotoxin and tubocurarine (active ingredient of curare) block acetylcholine receptors by preventing the opening of these ion channels. Following the release of acetylcholine, it is largely metabolized by hydrolysis, either within the synapses by acetylcholinesterase, or it is absorbed into plasma and then hydrolysed by butyrylcholinesterase. Drugs can act as agonists or antagonists at either muscarinic or nicotinic receptors.

Parasympathomimetics mimic the action of acetylcholine

Parasympathomimetics are a group of drugs that act either by directly stimulating the muscarinic receptor, for example pilocarpine, or by inhibiting the enzyme acetylcholinesterase, which hydrolyses the acetylcholine in the synapse.

Pilocarpine is used in the treatment of chronic open-angle glaucoma, facilitating aqueous drainage via its miotic action on the iris and contraction of the longitudinal muscle of the ciliary body. This draws on the scleral spur and opens the uveotrabecular meshwork. Parasympathetic stimulation has been shown experimentally to reduce aqueous outflow resistance with concomitant breakdown of the blood–aqueous barrier. Pilocarpine thus not only reduces outflow resistance but also reduces the rate of aqueous secretion. In addition, pilocarpine blocks the uveoscleral drainage route of aqueous (see Ch. 4, p. 35) so that drainage is confined to the canal of Schlemm. The ocular hypotensive effect of pilocarpine is further achieved by a reduction in blood flow within the ciliary body, which in turn reduces aqueous secretion (Box 6-13).

The side-effects of direct muscarinic agonists include conjunctival toxicity, iris cysts, cataracts and systemic absorption, which can give rise to muscarinic

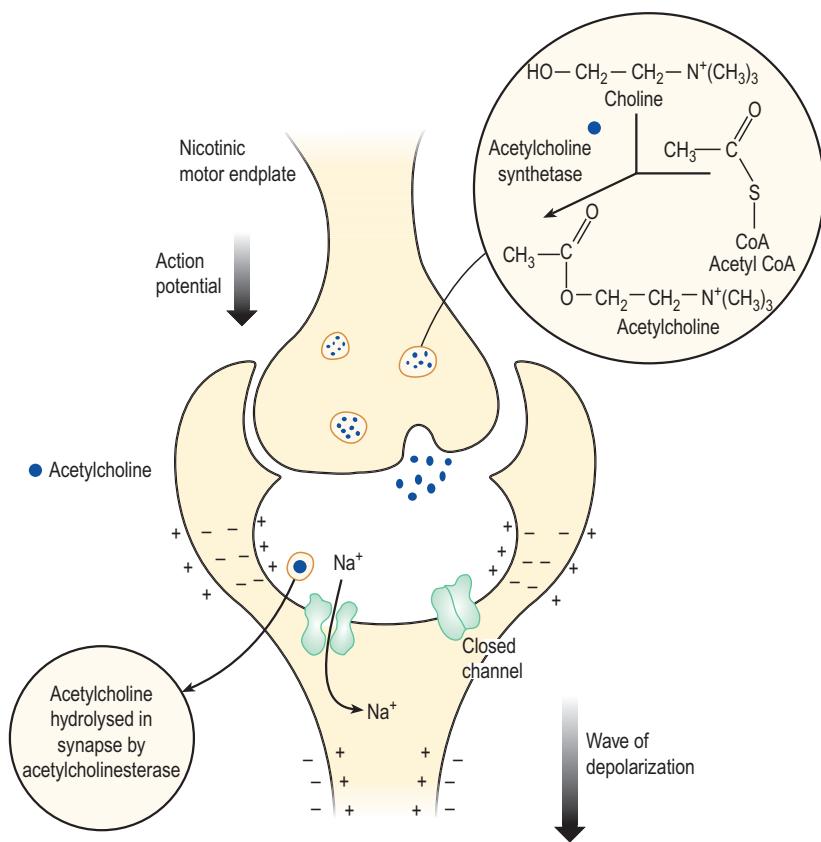


FIGURE 6-6 The parasympathetic system: motor endplate.

stimulation resulting in sweating, salivation, vomiting and bradycardia.

Parasympathetic antagonists affect the pupil and ciliary muscle separately and are exploited therapeutically

These drugs block the effect of acetylcholine at muscarinic receptor sites. Their principal effects are those of mydriasis (dilatation of pupil) and cycloplegia (inhibiting ciliary body muscle contraction), but additional effects also include reduction of lacrimal secretions (Table 6-1).

They are used clinically in the management of iritis (preventing adherence of the iris to the anterior capsule of the lens called posterior synechiae), for cycloplegic refraction, to facilitate routine fundal

BOX 6-13 USING PARASYMPATHOMIMETICS IN DIAGNOSIS

Edrophonium (a competitive inhibitor of acetylcholinesterase) is used in the diagnosis of ocular or systemic myasthenia gravis (tensilon test). After intravenous administration, any improvement in ptosis or diplopia confirms the diagnosis. Longer-acting anticholinesterases (neostigmine) can be used to maintain some neuromuscular function. Immunosuppressive therapies are also used to treat myasthenia because they impair the autoimmune response generated by the acetylcholine receptor antibodies.

Low concentrations of pilocarpine are used in the diagnosis of Adie's tonic pupil, by manifesting the miotic response of the supersensitive iris sphincter caused by loss of postganglionic nerve fibres in this condition.

examination and for the provocation test in narrow-angle glaucoma. The side-effects of this group of drugs are seen more often with the longer-acting drugs, for example atropine sulphate. Systemic absorption occurs, particularly with atropine, via conjunctival vessels and via nasal and nasopharyngeal mucosal absorption. Systemic side-effects include dry mouth, facial flushing, sweating and tachycardia. Ocular side-effects include hypersensitivity reactions and conjunctival hyperaemia, blurring of vision and photophobia,

a transient rise in intraocular pressure and, occasionally, precipitation of acute-angled glaucoma.

THE SYMPATHETIC SYSTEM

Acetylcholine, adrenaline (epinephrine) and noradrenaline (norepinephrine) all act as neurotransmitters within the sympathetic autonomic nervous system (Fig. 6-7). Acetylcholine is the neurotransmitter at autonomic ganglia, which includes the sympathetic nervous system. Adrenaline and noradrenaline are generated from hydroxylation of tyrosine to form DOPA, and further modified enzymatically to form dopamine, and finally adrenaline and noradrenaline (Fig. 6-8). Once released from the nerve ending they act on several well-defined subtypes of receptors. The action of the neurotransmitter is terminated by enzyme degradation with monoamine oxidases and catechol O-methyltransferase, and also by active reuptake into the nerve endings (Fig. 6-9). Understanding of sympathetic outflow facilitates the diagnosis of Horner syndrome.

Additional content available at <https://expertconsult.inkling.com/>.



TABLE 6-1 Antimuscarinic agents

Drug	Maximal mydriasis/ cycloplegia (min)	Duration
Atropine sulphate	40	7–10 days
Homatropine	40	1–2 days
Cyclopentolate	30	12–24 h
Tropicamide	20	3–4 h

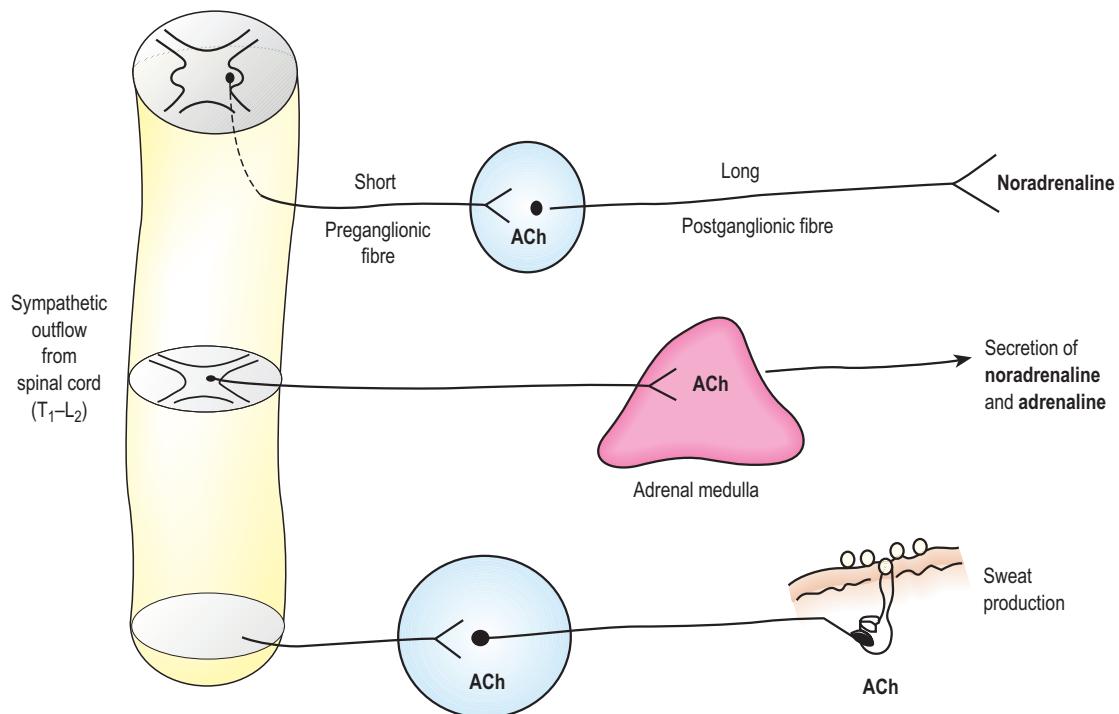


FIGURE 6-7 The sympathetic nervous system. ACh, acetylcholine.

Horner syndrome

Horner syndrome is important to recognize given that it can indicate life-threatening disease, for example Pancoast syndrome (apical lung tumour) or dissecting aortic aneurysm. The signs are a result of interference with sympathetic nervous system and anatomical diagnosis of location of pathology can be assisted with response to pharmacological block of sympathetic outflow.

CLASSICAL TRIAD OF SYMPTOMS

- Partial ptosis (loss of sympathetic innervation of Müller's muscle)
- Anhydrosis (decreased sweating affecting side of face)
- Miosis (loss of sympathetic tone to iris).

MAKING A DIAGNOSIS

Even with the advent of medical imaging to precisely locate the lesion within the sympathetic outflow pathway, diagnosis may be confirmed and then localized via pharmacological manipulation. The site depends on where the sympathetic outflow is perturbed.

- First order neurones – central lesions involving the medulla oblongata where autonomic centres reside (e.g. as seen in lateral medullary syndrome)
- Second order neurones – where preganglionic fibres are involved with compression of sympathetic chain (Pancoast syndrome)
- Third-order neurones – where postganglionic lesions at level of internal carotid artery (and within cavernous sinus) are affected.

THE USE OF DROPS

- Cocaine prevents the reuptake of noradrenaline, resulting in pupil dilatation. So in Horner syndrome with the loss of sympathetic drive, there is a failure of cocaine-induced pupil dilatation.
- Hydroxyamphetamine 1% will cause neurotransmitter release from the postganglionic fibres (third-order neurones). Therefore, in Horner syndrome affecting the preganglionic fibres, amphetamine will cause normal pupil dilatation, whereas if there is disruption of postganglionic fibres there will be no effect as there will be no noradrenaline to release.
- Both apraclonidine and phenylephrine drops will dilate postganglionic Horner syndrome due to denervation hypersensitivity.

The control of intraocular pressure is facilitated by similar and opposite effects of adrenergic receptors

(Box 6-14)

The control of intraocular pressure (IOP) and aqueous production and outflow has already been discussed (see Ch. 4, p. 222). It is well documented that certain α -agonists cause lowering of the IOP, for example clonidine, which is principally mediated by an α_2 -agonist action. On the other hand α_1 -agonists (e.g. phenylephrine) cause a rise in IOP with concomitant

pupillary dilatation. As α_2 -agonists produce an immediate fall in IOP, their effect is likely to be central, mediated by stimulation of the medullo pontine sympathetic centre. Conversely, α_1 -hypertensive effects are thought to be muscular in origin because the effect is antagonized by muscle relaxants.

β -receptors are the predominant receptor on ciliary epithelium, stimulation of which will reduce IOP experimentally. However, β -blockers (e.g. timolol) also reduce IOP. In humans, stimulation of β -receptors does not cause a reduction in aqueous secretion. Indeed adrenaline (a combined α - and β -agonist) causes an initial rise in IOP that is also associated with an initial rise in aqueous secretion. This effect is mediated by concomitant α_1 -receptor stimulation, the hypotensive effect being a purely α_2 -agonist action. Experimental evidence suggests that direct application of cAMP also increases aqueous drainage, and adenylyl cyclase, which is also activated by β_2 -agonists, produces a similar response. Certainly a rise in aqueous cAMP levels correlates well with reduction of IOP, which may be mediated by both α - and β -agonists, but as yet the exact mechanism is unknown (Box 6-15).

Additional content available at <https://expertconsult.inkling.com/>.

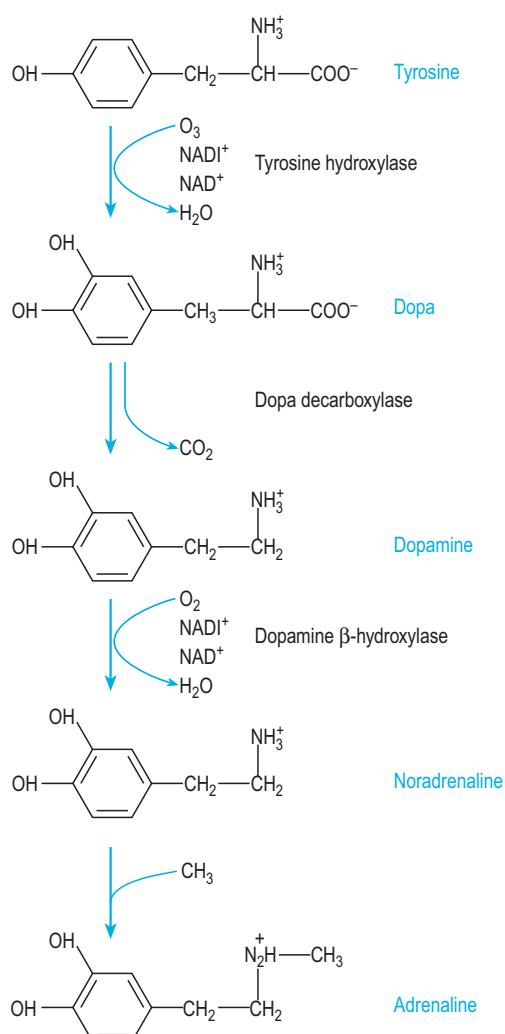


FIGURE 6-8 Synthesis of noradrenaline (norepinephrine) and adrenaline (epinephrine).

BOX 6-14 ADRENERGIC RECEPTORS

Adrenergic receptors are classes of G-coupled protein receptors of two types, α and β ; further subtypes exist within each group, classified according to the elicited response and distinguished by selective agonists and antagonists.

- α_1 -receptors mediate excitatory responses: principally smooth muscle contraction.
- α_2 -receptors are located mostly on the presynaptic nerve endings and are inhibitory because, when stimulated, they prevent further release of the neurotransmitter from the presynaptic terminal (Fig. 6-9).
- β_1 -receptors situated in the heart are excitatory and give rise to a positive inotropic and chronotropic response.
- β_2 -receptors can mediate inhibitory responses, relaxing the smooth muscle of blood vessels and bronchi.
- β_3 -receptors are located in adipose tissue and related to thermogenesis and lipolysis.

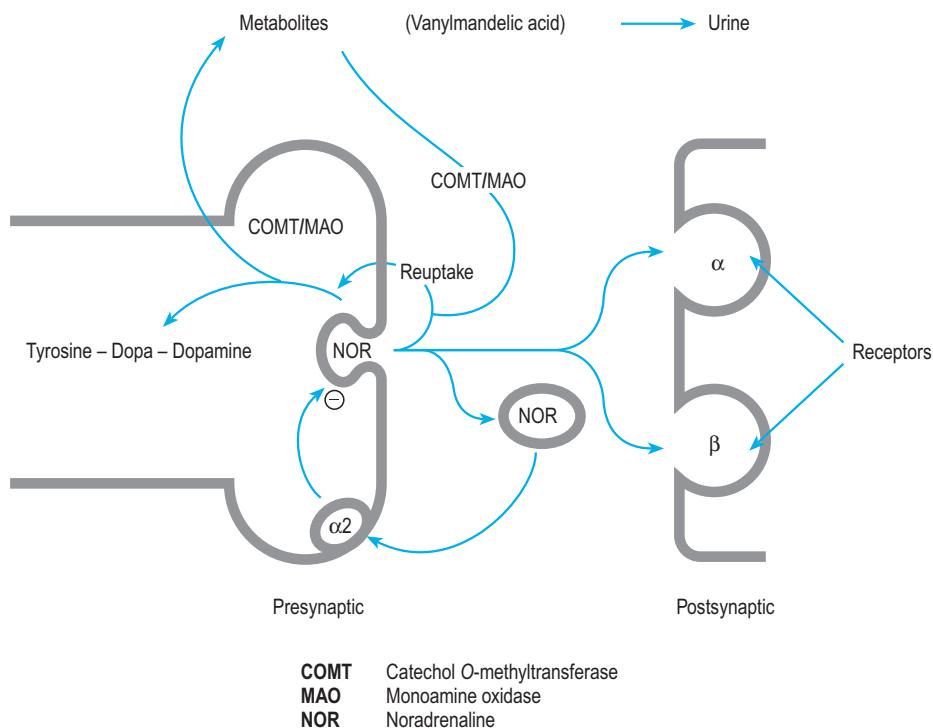


FIGURE 6-9 Adrenergic receptors and metabolism of adrenergic neurotransmitters.

BOX 6-15 ADRENERGIC ANTAGONISTS

NON-SELECTIVE β -BLOCKERS (β_1 AND β_2)

- Carteolol
- Levobunolol
- Timolol

SELECTIVE β_1 -BLOCKERS

- Betaxolol

Clinical control of intraocular pressure exploits the adrenergic system

Control of IOP is the main aim of therapy in primary open-angle glaucoma, a disorder that contributes greatly to the demands on eye health care systems. IOP control may be achieved surgically or medically and numerous topical therapies based on the pharmacology of the autonomic nervous system are in use, as described above.

However, medical treatment of glaucoma with respect to control of IOP may also be achieved by

systemic or local inhibition of carbonic anhydrase, an enzyme central to the formation of aqueous (see Ch. 4, p. 222), enhancing outflow pathways of aqueous flow or protecting the neurones (Box 6-16). The common drugs used topically are summarized in Box 6-17.

The ocular effects of adrenergic agonists include mydriasis, slight ciliary muscle relaxation (probably not relevant in humans), increased formation and increased outflow of aqueous humour (although a stimulation will decrease aqueous humour production), contraction of Müller's muscle and constriction of conjunctival and episcleral vessels (Table 6-2).

Additional content available at <https://expertconsult.inkling.com/>.



The histaminergic system: histamine is released from conjunctival mast cells during allergic reactions

Histamine is synthesized and stored in most tissues. It is derived from the amino acid histidine and excreted

ADRENERGIC AGONISTS

- Adrenaline stimulates both α - and β -receptors. Adrenergic receptors are found in cell membranes of iris dilator muscle, Müller's muscle, ciliary process epithelium and smooth muscle of ocular blood vessels. Phenylephrine is a synthetic sympathomimetic that acts directly on α -receptors. Mydriasis occurs within 1 hour and lasts 4–6 hours. The mydriasis of phenylephrine can be overcome by the powerful parasympathetic light reflex during fundoscopy. Thus, for maintained pupillary dilatation, a combination of phenylephrine and an antimuscarinic, for example cyclopentolate, is used. Systemic absorption is common with phenylephrine and care must be taken when using it in the elderly, in patients with hypertension, or in neonates and children.
- *Hydroxyamphetamine* acts by releasing noradrenaline from the nerve terminals. It is therefore used in the diagnosis of postganglionic Horner syndrome.
- *Cocaine*, whose membrane-stabilizing effect gives rise to its local anaesthetic properties, also prevents the reuptake of noradrenaline into the nerve endings, and is used in the diagnosis of pre- or postganglionic Horner syndrome in cases of anisocoria.
- *Apraclonidine hydrochloride* is a selective α -adrenergic agonist acting mainly on α_2 -receptors. It may be applied topically for the prevention and management of raised IOP after anterior segment laser treatment. It lowers IOP by decreasing aqueous humour formation. It does not penetrate the blood–aqueous barrier easily and therefore has minimal systemic side-effects, unlike clonidine.
- *Brimonidine* is a selective α_2 -receptor antagonist which over longer periods can reduce IOP without significant cardiovascular or pulmonary function effects.
- β_2 -adrenergic agonists also lower IOP, but their effect is mainly to increase the uveoscleral outflow, and they are often used in combination with β -blocking agents.

Commercially available L-adrenaline (Eppy 1%) can produce local irritation, allergy and adrenochrome deposits in the subconjunctiva. These adrenochrome deposits are most likely to be oxidative products of adrenaline and are most common in the palpebral conjunctiva. Dipivalyl adrenaline (Propine® 0.1%) is also used in the treatment of glaucoma. It is a lipophilic prodrug of adrenaline, and can penetrate into the anterior chamber, where it is hydrolysed into the active agent. If adrenaline or its prodrug analogues are used to treat aphakic glaucoma, there is a high incidence of cystoid macular oedema. This macular toxicity has been reported to occur in 20–30% of aphakic eyes undergoing adrenaline treatment. The mechanism of

cystoid macular oedema is unknown, but the angiographic features are identical to those of other conditions causing macular oedema, such as Irvine–Gass syndrome (vitreous–wound adherence following cataract surgery). Experimental evidence has shown that the high incidence of cystoid macular oedema in aphakic eyes is the result of higher concentrations of adrenaline in the retina of aphakic eyes (eTable 6-1).

ADRENERGIC ANTAGONISTS

Since the introduction of timolol maleate, topical β -blockers have become the most important therapeutic agents in the medical treatment of glaucoma. The lowering of IOP is a response to a blockade of β -adrenergic receptors in the ciliary epithelium, which produces up to 50% reduction in aqueous production. The site of action probably resides within the ciliary body, but it is not known whether adrenergic antagonists specifically affect ciliary body perfusion or the pumping mechanism of the ciliary epithelium. β -blockers certainly interact with β -adrenergic receptor-coupled adenyl cyclase of the ciliary epithelium. Clinically, there are now many β -blockers available, which vary according to their β -receptor selectivity. However, because of the opposing pharmacological actions of adrenaline and β -blockers, these drugs do not have an additive effect in lowering IOP. Timolol maleate is the most commonly used topical β -blocker and is non-selective, acting on both β_1 - and β_2 -receptors. Timolol binds reversibly with β -receptors and can reduce IOP in normal human eyes by reducing aqueous production by 15–48%. Betaxolol hydrochloride is a lipid-soluble β_1 -antagonist that is relatively cardioselective. It reduces IOP by decreasing the production of aqueous at the ciliary body, with no effect on aqueous outflow. Carteolol hydrochloride is a β -blocker that possesses intrinsic sympathomimetic activity, and is thought to be beneficial in glaucoma because it not only lowers IOP but also increases optic nerve head perfusion. Its intrinsic sympathomimetic activity does not appear to confer any protection from systemic side-effects of non-selective β -blockade. New β -blockers are frequently under investigation for their effectiveness in reducing IOP and preventing the progression of glaucomatous visual field loss. The ideal β -blocker would block β -receptors in the eye without having any effect on systemic β -receptors.

Systemic side-effects of agonist agents include hypotensive episodes, cardiac arrhythmia, headache and anxiety. The systemic effects of β -blockade include bronchospasm, bradycardia, syncopal attacks and central nervous system depression. It is still not confirmed whether systemic absorption of β -blockers raises levels of serum triglycerides and cholesterol, as with systemic β -blockade, which is of particular importance when treating patients with ischaemic heart disease or more widespread vascular disease.

eTABLE 6-1 Sympathomimetic drug receptor profile/action

Sympathomimetic	Receptor/action
Noradrenaline	α and β
Adrenaline	α and β
Phenylephrine	α (non-selective)
Brimonidine	Selective α_2 -agonist
Apraclonidine	α_2 partial agonist
Hydroxyamphetamine	Releases noradrenaline from nerve endings; inhibits monoamine oxidases
Cocaine	Inhibits uptake of noradrenaline at nerve endings

Carbonic anhydrase in the eye is a target enzyme for drug action

Aqueous humour is secreted actively into the posterior chamber by the non-pigmented epithelium of ciliary processes, which in turn is dependent on the active transport of sodium using the sodium/potassium ATPase pump (see Ch. 4, p. 257). Aqueous secretion can be decreased by inhibiting bicarbonate formation, an essential component in aqueous production. The production of bicarbonate is catalysed by the ubiquitous enzyme carbonic anhydrase, which exists in at least six isoforms. Carbonic anhydrase catalyses the hydration of carbon dioxide to bicarbonate, which then dissociates to form hydrogen ions and bicarbonate. The subtypes of carbonic anhydrase enzymes located in ocular tissues include carbonic anhydrase isoenzyme II, which is found in the ciliary body, and isoenzyme IV, which is thought to be a membrane-bound fraction of the enzyme found in the apical region of the RPE cells. Inhibition of carbonic anhydrase reduces aqueous production. This may be a direct effect of enzyme inhibition or secondary to the altered intracellular pH and blockade of the sodium/potassium ATPase ion channel. The effect of acetazolamide therapy is perhaps somewhat surprising. Carbonic anhydrase has a high turnover and the drug must not only reach the active site but also remain in high enough concentrations to have a sufficient duration of action. The drug binds avidly to red blood cell carbonic anhydrase and, when saturation is reached, the drug may effectively distribute to other tissue-binding sites, e.g. ciliary processes and proximal tubule of the kidney. Carbonic anhydrase inhibitors are useful in selected cases of glaucoma. However, these drugs are usually sulphonamide derivatives and can have severe systemic side-effects, including potassium depletion, dermatitis, renal stones (the incidence is said to be 11 times higher than normal), acidosis and, most commonly, fatigue and paraesthesia of the extremities, which can make up to 50% of patients intolerant to its long-term use. Acetazolamide is the most frequently used agent, and recently a new sustained-release preparation has become available which is said to reduce the incidence of systemic side-effects. Dorzolamide is a topical carbonic anhydrase inhibitor used to lower IOP in patients resistant or intolerant to β -blockers. It is irritant to the corneal and conjunctival surface and systemic absorption may rarely give rise to sulphonamide-like side-effects.

BOX 6-16 PROTECTING NERVE FIBRES WITHOUT LOWERING IOP: NEUROPROTECTION

- *Glutamate-receptor blocking agents* – reduce excessive calcium influx and ATP synthesis inhibiting excitatory cell death. Agents may act at different sites (receptors) inducing amino acid-induced excitotoxicity.
- *NMDA (N-methyl D-aspartate) receptor inhibition* – NMDA is a postsynaptic ligand-gated ion channel requiring NMDA and glycine for activation. Antagonists can either be competitive or non-competitive, both of which ultimately reduce glutamate secretion and reduce excitotoxicity.
- *Nitric oxide synthase inhibition*
- *Antioxidants*

BOX 6-17 ACTIONS OF TOPICALLY APPLIED DRUGS THAT LOWER IOP

- β -blockers (timolol, betaxolol, levobunolol, carteolol) decrease aqueous production by up to 50% and thus lower IOP, even in normal eyes. Their precise action remains unknown but they are likely to affect either vascular perfusion of the ciliary body or adenyl cyclase of the ciliary epithelium.
- Parasympathomimetics (pilocarpine) lowers IOP by facilitating aqueous outflow via its direct action on the scleral spur and ciliary body muscle.
- α_2 adrenostimulants (brimonidine and apraclonidine) stimulate receptors in the trabecular meshwork (increasing both intracellular and aqueous cAMP levels), which increases the facility of outflow. Stimulation of the α -receptors on blood vessels supplying the ciliary body causes vasoconstriction and reduced blood flow, and consequently reduced aqueous production.
- Prostaglandin analogue (latanoprost, travoprost) is a prostaglandin $F_{2\alpha}$ analogue and a prostanoid FP receptor (Gprotein-coupled receptor) agonist, which reduces IOP by increasing the outflow of aqueous humour, mainly uveoscleral outflow.
- Carbonic anhydrase inhibitors (systemic – acetazolamide – or topically – brinzolamide, dorzolamide).

in the urine after being enzymatically degraded in the liver by histaminase. Histamine is a modulator of the inflammatory response, particularly in allergic type I hypersensitivity reactions (see Ch. 7, p. 445). Histamine also plays an integral role in neurotransmission, for example regulating gastric acid secretion. Four

TABLE 6-2 Profile of adrenergic receptors in the eye

	α	β
Iris dilator	+++	+/-
Iris sphincter	+/-	+
Ciliary process epithelium	+/-	+++
Conjunctival blood vessels	+	+
Müller's muscle	+	-

BOX 6-18 HISTAMINE RECEPTOR ANTAGONISTS

- H_1 – diphenhydramine, loratadine, cetirizine
 H_2 – ranitidine, cimetidine
 H_3 – ciproxifan
 H_4 – thioperamide

common histamine receptors (7 transmembrane Gprotein-coupled receptors) are described, H_1 – H_4 on the basis of the structure of the specific antagonist that binds to them (Box 6-18).

H_1 -receptors are found in abundance in human bronchial muscle and at many other sites, including the CNS. The histamine receptors in these tissues have the same affinity for histamine as for the histamine-competitive antagonist cetirizine. H_2 -receptors are found in the stomach, heart and uterus. The receptors involved have a common affinity for the competitive histamine antagonist cimetidine. Activation of H_1 -receptors results in an increase in intracellular calcium concentration, and activation of H_2 -receptors results in stimulation of adenyl cyclase and second messenger production (Box 6-19).

Mast cells are an abundant source of histamine. Histamine release is mediated by allergen-induced immunoglobulin E (IgE) hypersensitivity responses. Control of this allergic response can be obtained by preventing mast cell degranulation at the mucous membranes with mast cell stabilizing agents. This is of particular relevance when considering the management of allergic eye disease (Box 6-20).

ANTIHISTAMINES

H_1 antihistamines inhibit histamine-induced contraction of smooth bronchial muscles and increased

BOX 6-19 ACTIONS OF HISTAMINE

H₁ ACTIONS

- Increases vascular permeability and vasodilatation of arterioles
- Arteriolar dilatation of superficial skin vessels (axon reflex)
- Capillary dilatation and oedema of dermis
- Smooth muscle contraction/bronchospasm
- Increased mucus secretion
- Central nervous system depressant

H₂ ACTIONS

- Increased pepsin and acid production
- Increased myocardial stroke volume

H₃ ACTIONS

- Receptors associated with neural tissue at presynaptic sites, which, when stimulated, inhibit histamine release, the significance of which is unclear

H₄ ACTIONS

- Mediates mast cell chemotaxis and calcium mobilization in mast cells

BOX 6-20 TREATING ALLERGIC EYE DISEASE

TOPICAL ANTIHISTAMINES

- Azelastine
- Levocabastine

MAST CELL STABILIZERS

- Sodium cromoglicate
- Lodoxamide

vascular permeability caused by histamine. Some H₁ antagonists have pronounced central nervous system side-effects, including drowsiness, but also have the benefit of being antiemetics. Recently introduced H₁ antihistamines have markedly reduced sedative or anticholinergic action and do not so readily cross the blood–brain barrier when administered systemically.

H₂ antagonists are effective in the pharmacological control of gastric acid secretion by decreasing basal and food-stimulated acid secretion (up to 90%). The two drugs commonly used are cimetidine and ranitidine, which are structural analogues of histamine. Cimetidine also inhibits cytochrome P₄₅₀ and decreases the metabolism of drugs (e.g. anticoagulants, phenytoin and aminophylline), thus potentiating their effects. Cimetidine binds to androgen receptors,

sometimes leading to gynaecomastia and reduced sexual function.

SODIUM CROMOGLYCATE

Disodium cromoglycate is used in the treatment of allergic hypersensitivity reactions and is administered topically, either into the conjunctival fornix or by inhalation to the bronchial mucosa. It acts by inhibiting the release of histamine and slow-releasing substance of anaphylaxis (SRS-A) from the mast cells within the mucosa, by stabilizing mast cell membranes. It must therefore be administered before mast cell priming with IgE and allergen because it will have no effect once the mast cells have degranulated. Lodoxamide has also been developed as a topical application to prevent mast cell degranulation, alongside increasing numbers of topical choices in this class of agent.

Eicosanoids affect multiple ocular functions

Eicosanoids are not found preformed in tissues but are generated *de novo* from cellular phospholipids after a wide range of stimuli. They are important mediators of the inflammatory response, and the non-steroidal anti-inflammatory drugs (NSAIDs) owe some of their activity, especially prostaglandin F_{2α}, to the inhibition of the synthesis of eicosanoids. The name prostaglandin derives from reports that semen contained a substance that contracted the uterus and was thought to be derived from the prostate gland. However, the first prostaglandins were described in the eye, although not named as such.

The principal eicosanoids are the prostaglandins, thromboxanes and leukotrienes (see Ch. 7, p. 394). The main source of these substances is from the 20-carbon unsaturated fatty acid arachidonic acid, which is found esterified in the phospholipids of cell membranes. Figure 6-10 describes the generation of these molecules, where the initial rate-limiting step is the generation of arachidonate by phospholipase A₂ or C. Stimuli that liberate these enzymes include thrombin in platelets, C5a from complement and bradykinin, as well as general cell damage. The free arachidonic acid is then metabolized via two pathways mediated by the enzymes cyclo-oxygenase, generating

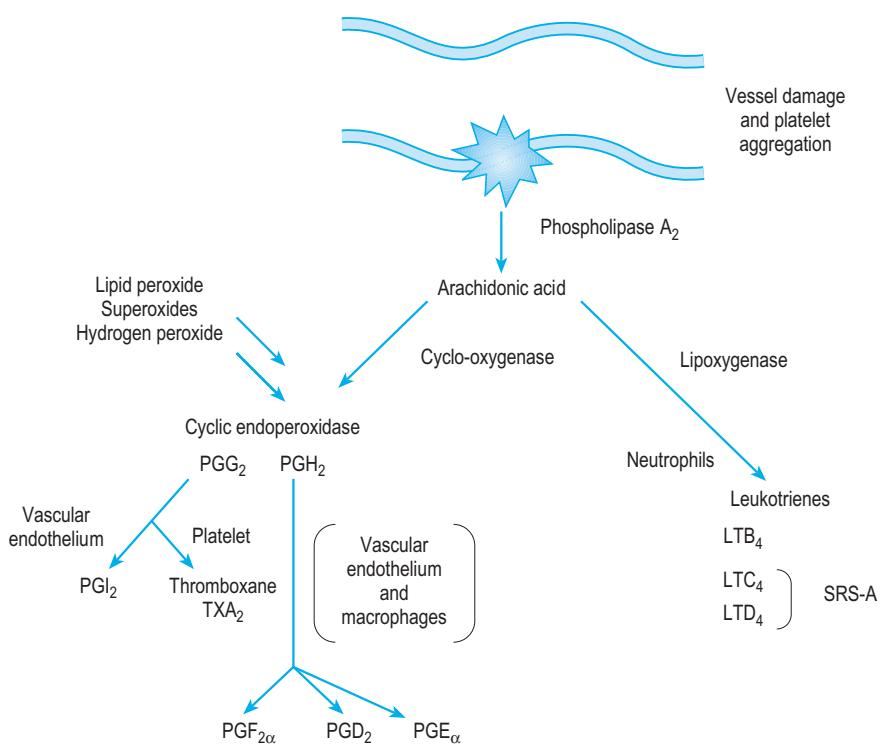


FIGURE 6-10 Synthesis of eicosanoids.

prostaglandins, and lipoxygenase, generating leukotrienes (see Ch. 7, p. 394). The anti-inflammatory action of the NSAIDs is mainly the result of the inhibition of cyclo-oxygenase, and thus prostaglandin synthesis (Box 6-21).

Each prostaglandin appears to act on specific receptors which have yet to be fully characterized. However, receptor antagonists are gradually being developed for each eicosanoid. A recent example is misoprostol, which reduces gastric acid secretion and gastric erosion by NSAIDs, by the antagonism of prostaglandin E₂ class 1 receptors.

Aspirin, among other compounds, inactivates cyclo-oxygenase and reduces inflammation and pain. Other systemically administered NSAIDs, such as indometacin and flurbiprofen, are used in an attempt to reduce the inflammatory response in uveitis and scleritis. Indometacin is used also to reduce cystoid macular oedema, but its effects have yet to be substantiated. Both ibuprofen and diclofenac are now available as topical applications; their principal use is to

BOX 6-21 BIOLOGICAL ACTIONS OF EICOSANOIDS

PROSTAGLANDINS

- Prostaglandin I₂ – vasodilatation, decreases platelet adhesion
- Prostaglandin F_{2α} – bronchial smooth muscle contraction
- Prostaglandin E₂ – vasodilatation, bronchodilatation, uterine contraction, pyretic, stimulates release of pituitary hormones, adrenal cortex steroids and insulin from pancreas, macrophage activation

THROMBOXANE

- Thromboxane A₂ – vasoconstriction, platelet aggregation, bronchoconstriction

LEUKOTRIENES

- Leukotriene B₄ – aggregation of neutrophils, chemotactic, stimulation of phospholipase A₂
- Leukotriene C₄
- Leukotriene D₄ – contraction of smooth muscle, bronchoconstriction, vasoconstriction, leukotrienes C₄ and D₄ together form SRS-A.

prevent perioperative miosis during cataract surgery as well as to reduce postoperative inflammation.

More recently, prostaglandin analogues have been studied for use in primary open-angle glaucoma, e.g. prostaglandin F_{2α}.

In an attempt to increase the efficacy of NSAIDs and reduce, in particular, gastric mucosal erosions, newer NSAIDs are being generated which are specific for one of the isoenzymes of cyclo-oxygenase, cyclooxygenase 2 (COX-2). COX-2 specificity is said to confer a more specific inhibition of inflammatory prostaglandin synthesis, without impairing synthesis of gastroprotecting prostaglandins, e.g. prostaglandin I₂, which is synthesized by COX-1. Conventional NSAIDs are strong inhibitors of COX-1 and less active against COX-2.

Serotonin: a potent neurotransmitter

Neurotransmitters are integral to retinal and cortical function, and drugs that modulate their function may alter visual perception. In addition, some neuromodulatory drugs are used to treat conditions with visual symptoms, such as migraine.

5-Hydroxytryptamine (5-HT; serotonin) is biosynthesized in a manner similar to noradrenaline from the precursor amino acid tryptophan, which is taken up into the nerve endings and converted by tryptophan hydroxylase to 5-hydroxytryptophan, and then decarboxylated to serotonin. Serotonin is degraded by oxidative deamination by the action of a group of enzymes called *monoamine oxidases* to form the aldehydes 5-hydroxyindoleacetaldehyde and 5-hydroxyindoleacetic acid (5-HIAA), analogous to noradrenaline metabolism. The aldehydes are then excreted in the urine and may be detected in hypersecretory conditions such as carcinoid syndrome.

SEROTONIN RECEPTOR SUBCLASSES MEDIATE DIFFERENT EFFECTS

Serotonin is a neurotransmitter that is widely distributed throughout the body, particularly in platelets, mucosa of the gastrointestinal tract and neurones of both the central and peripheral nervous system. There are four main types of serotonin receptors, designated 5-HT₁, 5-HT₂, 5-HT₃ and 5-HT₄. Although 5-HT is a simple molecule, it has a wide variety of effects in the

cardiovascular, gastrointestinal, respiratory and central nervous systems.

5-HT₁-receptors can be further divided into subtypes 5-HT_{1a-d}. They are differentiated by the kinetics of agonist and antagonist binding to the receptor, and by their regional distribution within the central nervous system. 5-HT_{1a} has been found in the raphe nucleus and the hippocampus, activation of which causes hypotensive attacks and behavioural changes. This has been studied with particular reference to the physiology of anxiety. 5-HT_{1b} is found in rodents and is thought to have an inhibitory effect on the release of 5-HT, similar to the 5-HT_{1d}-receptor in humans. 5-HT_{1c} has been localized to the choroidal plexus, but no specific agonist or antagonist has yet been identified. The 5-HT₂-receptor is located in the hippocampus, frontal cortex and spinal cord. These receptors are also located on smooth muscle in the bronchus and blood vessels. They have a direct excitatory effect on smooth muscle. 5-HT₃-receptors are found in the nerves along the gastrointestinal tract and peripheral nervous system. 5-HT exerts an excitatory effect through these receptors, particularly excitation of nociceptive nerve endings. They are also found in the limbic and cortical areas of the brain, and are thought to play an important role in the development of anxiety and psychotic states. Recently 5-HT₄-receptors have been discovered in the CNS but their clinical significance remains unclear.

5-HT ANTAGONISTS

Selective 5-HT₂-receptor antagonists, which are used for the prevention of migraine attacks (e.g. methysergide and pizotifen), probably act by inhibiting the release of serotonin at the aura stage of the attack. During this stage the activation of 5-HT neurones is at its greatest, and thus antagonism of the receptors prevents the sequelae of vascular smooth muscle contraction, local inflammation and nociceptor stimulation. Selective 5-HT₃-receptor antagonism (e.g. ondansetron) reduces the 5-HT nociceptive stimulation, and thus the headache of migraine.

Glucocorticoids

Steroids are applied topically to suppress the inflammatory reaction of many conditions, commonly

anterior uveitis, postoperative inflammation and corneal graft rejection. They may also be administered subconjunctivally or systemically in more severe intraocular inflammatory conditions. The mechanism of their anti-inflammatory actions is mediated by the drug's effects on both the number and function of lymphocytes, polymorphonuclear leucocytes and macrophages, and on vascular permeability. They also affect inflammatory mediators by inhibiting phospholipase A₂, prostaglandin, thromboxane and leukotrienes; and they also inhibit histamine release. Despite the pleotropic and what at first seems significantly powerful anti-inflammatory effects, steroids have many ocular side-effects, including cataract formation, reactivation of viral keratitis or increased incidence of bacterial infection, and steroid-induced rises in IOP. The latter side-effect is dependent on the duration and strength (potency) of individual steroid preparations as well as genetic predisposition.. The rise in IOP is thought to occur via the accumulation of glycosaminoglycans and water in the trabecular meshwork, reducing aqueous outflow. Thirty per cent of normal subjects have a hypertensive response when challenged with corticosteroids. This can be characterized further into poor responders, moderate responders (heterozygous responders) and strong responders (homozygous responders). If the individual also has open-angled glaucoma, a greater overall response is seen. It is therefore important that IOP is monitored at regular intervals during the course of prolonged steroid therapy.

The anti-inflammatory potency of any particular steroid is dependent on its ability to penetrate the cornea. Increasing the steroid concentration results in higher intraocular concentrations, but this may also be achieved with different formulations of the same parent steroid that increase the contact time of the topically applied drug. Steroids such as prednisolone phosphate are hydrophilic and therefore penetrate the corneal epithelium poorly; in contrast, the acetate forms of both dexamethasone and prednisolone give rise to a much greater intraocular concentration. To date, it is still not established which concentrations of steroids are desirable for low-grade intraocular inflammatory conditions. If this could be established, ocular side-effects might be kept to a minimum.

Immunosuppressant agents: combating ocular inflammatory disease

Controlling immune responses, particularly T-cell responses (Ch. 7, p. 395), that mediate allograft rejection, endogenous uveitis, associated or not with other autoimmune conditions, and chronic allergic eye disease may necessitate systemic therapy with immunosuppressants. In addition to steroids, there is now a significant armamentarium of agents used in ophthalmology to treat such conditions. Such agents have been generated as a result of our increased understanding of T-cell biology, in particular the interactions of T cells with specific antigens and antigen-presenting cells, activation of T cells and the effects of mediators of inflammation, such as cytokines.

Commonly used agents in addition to the traditional use of steroids for suppressing inflammatory responses (Box 6-22), include cyclosporin A, purine antagonists and cytotoxic agents such as methotrexate, and occasionally alkylating agents such as cyclophosphamide. Newer generations of similarly acting agents are now used, especially in prevention of solid organ allograft rejection, including tacrolimus (FK 506) and mycophenolate mofetil (CellCept®). The mechanism of action of such agents and its effect on T-cell activation are represented in Figure 6-11.

Although successful, immunosuppressive therapy is limited by its relative non-specificity, the refractivity of some patients to therapy and the high incidence of side-effects (Box 6-23). To reduce unwanted

BOX 6-22 IMMUNOSUPPRESSANTS AND THEIR MODE OF ACTION

- **Corticosteroids** – act on cytosolic receptors and block transcription of cytokine genes (e.g. interleukins 1, 2, 3 and 5, tumour necrosis factor- α and interferon- γ)
- **Cyclosporin** – acts via inhibition of calcineurin and NFAT, resulting in inhibition of interleukin-2 production
- **Tacrolimus** – inhibits interleukin-2; mechanism similar to cyclosporin
- **Azathioprine** – inhibits purine synthesis, blocking RNA and DNA synthesis
- **Methotrexate** – folic acid antagonist, inhibiting dihydrofolate reductase and suppressing DNA synthesis
- **CellCept** – blocks *de novo* pathway of purine synthesis, which is selective for lymphocytes

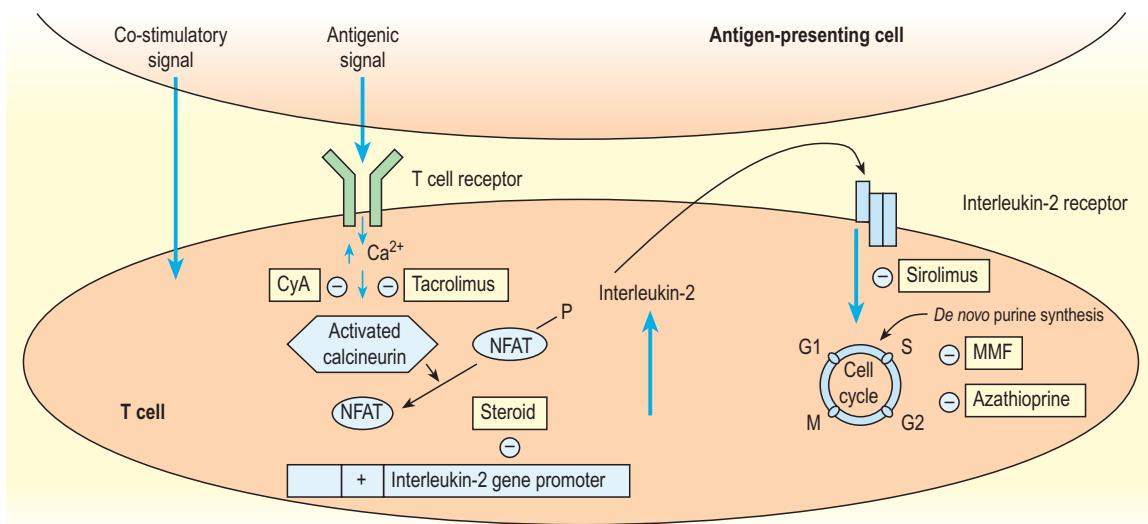


FIGURE 6-11 Stages of T-cell activation: multiple targets for immunosuppressive agents. Signal 1: stimulation of T-cell receptor (TCR) results in calcineurin activation, a process inhibited by ciclosporin (CyA) and tacrolimus. Calcineurin dephosphorylates nuclear factor of activated T cells (NFAT), enabling it to enter the nucleus and bind to interleukin-2 promoter. Corticosteroids inhibit cytokine gene transcription in lymphocytes and antigen-presenting cells by several mechanisms. Signal 2: co-stimulatory signals are necessary to optimize T-cell interleukin-2 gene transcription, prevent T-cell anergy and inhibit T-cell apoptosis. Experimental agents but not current immunosuppressive agents interrupt these intracellular signals. Signal 3: interleukin-2 receptor stimulation induces the cell to enter the cell cycle and proliferate. Signal 3 may be blocked by interleukin-2 receptor antibodies or sirolimus, which inhibits the second messenger signals induced by interleukin-2 receptor ligation. Following progression into the cell cycle, azathioprine and mycophenolate mofetil (MMF) interrupt DNA replication by inhibiting purine synthesis. (From Denton et al., 1999, with permission from Elsevier.)

BOX 6-23 COMMON SIDE-EFFECTS OF IMMUNOSUPPRESSANTS

- *Corticosteroids* – osteoporosis, hypertension, glucose intolerance, altered habitus
- *Ciclosporin and tacrolimus* – nephrotoxicity, hypertension, hyperlipidaemia, glucose intolerance, hirsutism and gingival hyperplasia
- *Azathioprine/CellCept* – bone marrow suppression, diarrhoea and gastrointestinal upset

systemic effects, some agents, for example ciclosporin A and tacrolimus, are currently being formulated for topical delivery to treat chronic allergic disease and corneal allograft rejection.

BIOLOGICS

The current expertise in molecular biological and engineering technology has permitted over the past decade the generation of specific molecules that can be engineered to specifically target receptors,

membrane proteins or soluble proteins. With reference to eye diseases, this has resulted in newer treatments for ocular inflammatory disorders and retinal choroidal angiogenesis such as 'wet' age-related macular degeneration, as discussed earlier. For example, one of the principal mediators of T-cell responses in autoimmune disorders, such as rheumatoid arthritis, inflammatory bowel disease and posterior uveitis, is tumour necrosis factor- α (TNF- α). Engineering either specific antibodies or immuno-oadhesins (fusion proteins of their receptors bound to a human immunoglobulin tail) can recognize membrane-bound and soluble TNF- α and neutralize its activity. TNF- α binds two receptors (p55-TNFR1 or p75-TNFR2). The commercially available biologics include *infliximab*, a chimeric antibody (human with mouse-derived variable region recognizing TNF- α) or *Humira®* (a humanized monoclonal antibody) that inhibits TNF- α by neutralizing both membrane-bound and soluble TNF and *etanercept*, which is

a fusion protein of p75 receptor that successfully binds TNF, thereby preventing further binding (Fig. 6-12). There are now many targets that can be specifically inhibited with monoclonal antibody or other biological therapy (Fig. 6-13).

Local anaesthetics: an integral part of ophthalmic examination and surgery

Local anaesthetics consist biochemically of an aromatic residue linked to an amide or basic side-chain. As such, local anaesthetics are both hydrophobic (aromatic residue) and hydrophilic (amide group), and tend to accumulate at aqueous–non-aqueous interfaces. Because the aromatic residue and side-chain in some local anaesthetics are linked by esters, they are

susceptible to metabolic hydrolysis. These compounds are usually inactivated in the liver and plasma by non-specific esterases. As amide links are more stable, this group of anaesthetics has a longer $t_{1/2}$.

LOCAL ANAESTHETICS AFFECT EXCITABLE MEMBRANES

Local anaesthetics block the initiation and propagation of action potentials by preventing the voltage-dependent increase in sodium conductance via a direct action on sodium channel function and, to a lesser degree, by stabilizing membranes. The action of local anaesthetics is strongly pH dependent. Under alkaline conditions the proportion of the local anaesthetic that is ionized is low but it is also lipid-soluble. This allows the anaesthetic to penetrate the myelin of

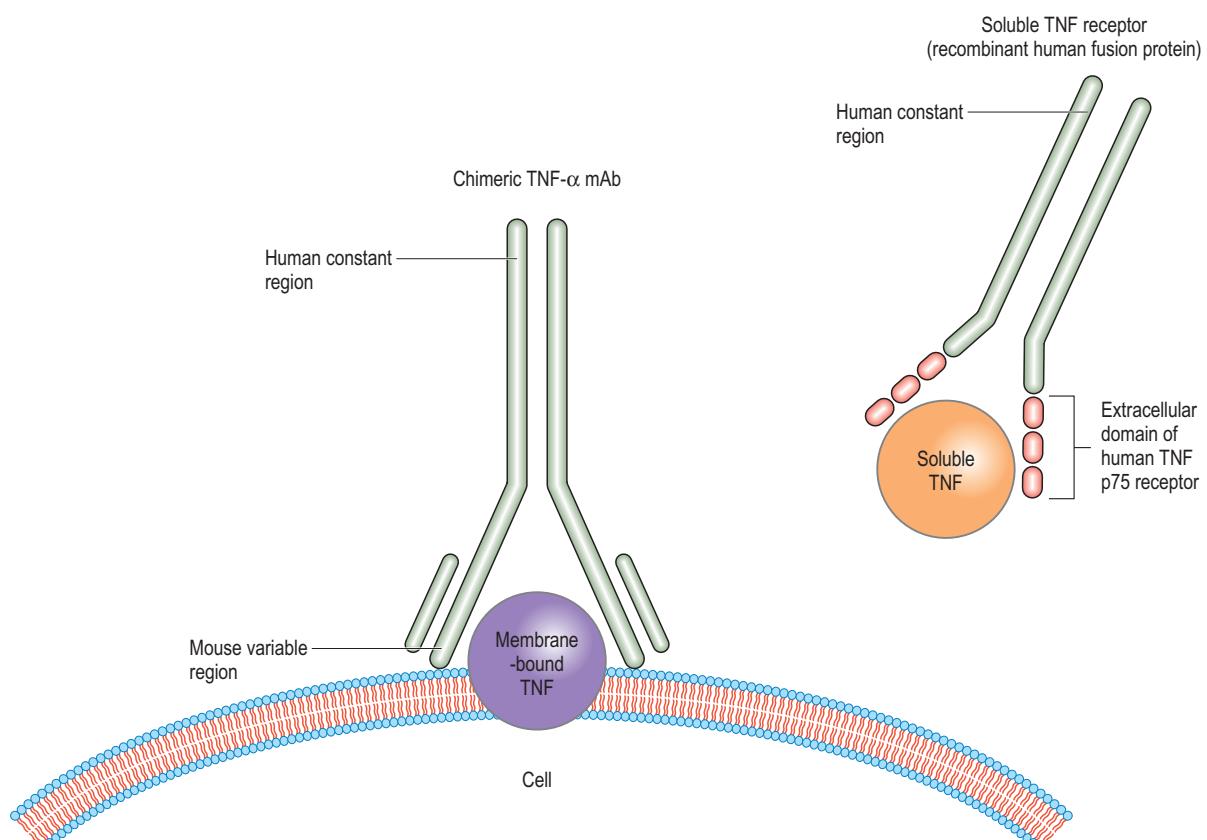


FIGURE 6-12 Schematic representation of anti-TNF agents infliximab and the fusion protein etanercept. (From Cochrane and Dick, 2007, with permission from Springer Science and Business Media.)

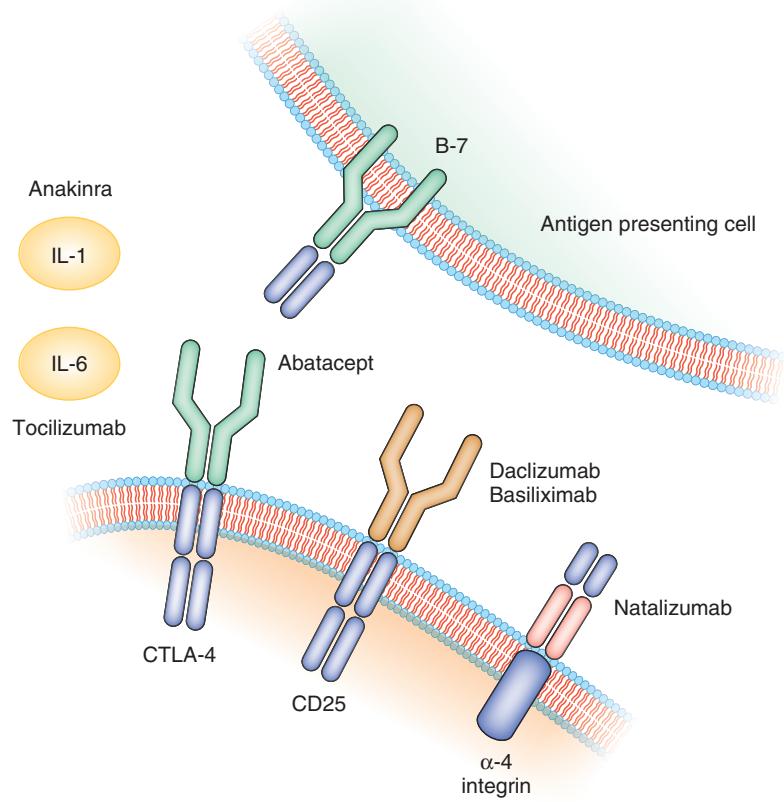


FIGURE 6-13 Biologics target key mediators of inflammation. Chimeric or humanized monoclonal antibodies or fusion proteins can deliver potent inhibition of cell response and inflammation. The schematic shows some currently available targets and biological therapies that have been generated and are being brought into practice for the treatment of inflammatory eye diseases.

the medullated nerve fibres. However, once inside the myelin sheath, the ionized cationic form of the drug is the active species, giving rise to the local anaesthetic effect. If the local anaesthetic is unable to penetrate the myelin sheath, its action can be mediated only via the node of Ranvier at several sites along the nerve. However, in unmyelinated fibres only a short length of fibre needs to be functionally interrupted to induce anaesthesia. In general, local anaesthetics block small-diameter nerves (myelinated more than unmyelinated) more readily, but practically it is not possible to produce a block of pain sensation without affecting other modalities, and there is no inherent difference between the susceptibility of motor and sensory nerves to local anaesthetics.

Local anaesthetics used in ophthalmology are usually aromatic residues linked to tertiary amide

chains. These agents are more stable in acidic solutions where they are in their cationic form. However, when applied to the conjunctival sac and orbital tissues (pH 7.4), only 15% will be in the non-cationic form and lipid soluble, allowing the drug to penetrate myelin. Topical application of the anaesthetic blocks parasympathetic and sympathetic fibres first, followed by sensory (pain and temperature), and finally motor (large, myelinated) nerves.

During infiltrative regional anaesthesia for surgery (e.g. peribulbar or subtenons anaesthesia for intraocular surgery) a 1:200 000 concentration of adrenaline may be added to constrict blood vessels and retard vascular absorption and hydrolysis of the agent. Adrenaline is inactivated by heat, so may have reduced potency in precombined formulations. In addition, the pH of the local anaesthetic may be altered when

mixing with an adrenaline solution which itself is acidic. This results in a reduced amount of the non-cationic form that is able to penetrate medullated nerve fibres.

LOCAL ANAESTHETICS HAVE BOTH LOCAL AND SYSTEMIC SIDE-EFFECTS

Topically applied anaesthetic agents are well recognized as inhibitors of wound healing. They disrupt tight junctions between cells and interfere with corneal epithelial metabolism and, ultimately, the repair of corneal epithelial wounds. Systemic effects include numbness and tingling, dizziness, slurred speech and aggressive behaviour (Box 6-24). Central nervous system toxicity may ultimately lead to convulsions with respiratory and myocardial depression. In the UK it has been recommended by the Royal College of Ophthalmologists that intravenous access (an infusion line) is available and monitoring of both heart rate and oxygen saturation is performed during infiltrative regional local anaesthesia.

Ocular toxicity from systemic administration of drugs

Ocular side-effects from the systemic administration of drugs are well recognized (see above in relation to glaucoma treatment and the use of topical steroids). Access to the globe by systemically administered drugs is restricted by the blood-retinal and blood-aqueous barriers, as stated above. In the absence of ocular inflammation, penetration of the drug into the eye is a function of the drug's physicochemical properties.

BOX 6-24 MAXIMAL SAFE DOSES OF REGIONAL LOCAL ANAESTHETICS

LIDOCAINE

- 10–15 mL 2% solution (200 mg)
- 20–25 mL 2% solution with adrenaline, 1:200 000 (500 mg)

BUPIVACAINE

- 15–20 mL 0.75% solution (150 mg)

Drugs or their active metabolites may accumulate in the eye, particularly within the melanin of the uveal tract, the cornea (because of its differential solubility characteristics) and the lens.

UVEAL TRACT

Some drugs possess a high affinity for binding to melanin, from which they are only slowly released. A good example of this is chloroquine, which is known to concentrate in the melanin of the RPE and persist in this tissue for prolonged periods. If chloroquine is taken in large enough doses and for a long duration, the drug-melanin complex will result in retinal toxicity, although the exact mechanism remains unknown. The mechanism of drug binding to melanin is complex and involves electrostatic (van der Waals') forces as well as possible cation exchange, which may displace free radicals from the melanin and, in turn, give rise to retinal toxicity. However, binding of the drug alone is not sufficient to give rise to retinal toxicity. For instance, β -blockers and benzodiazepines are irreversibly bound to melanin, although the amount of bound drug does not correlate with the damage to the RPE or uveal tract. Indeed, phospholipid metabolism within the RPE is still normal after 6 months of chloroquine treatment. In the case of chloroquine, the retinopathy is seen usually in patients receiving more than 100 g total dose of drug or in patients taking the drug for more than 1 year. In general there is a low incidence of retinal toxicity from hydroxychloroquine, and some centres regard this drug as safe and not requiring monitoring of patients.

PHOTOSENSITIZATION

Photosensitizing agents absorb visible and ultraviolet radiation and, as a result, generate free radicals (see Ch. 4, p. 193). These photosensitizing agents may become bound to macromolecules in the cornea, lens and retina. Amiodarone, phenothiazines and psoralens are well-known examples of photosensitizing agents. The cornea, lens and retina may also act as drug depots. For example, once the therapeutic agent has circulated through the uveal tract into the aqueous it can rapidly penetrate the corneal endothelium and deposit in the stroma or, if lipophilic, accumulate in the corneal epithelium.

Oculotoxic drugs

Examples of oculotoxic drugs include steroids and ethambutol. Long-term steroid treatment is well recognized as a cause of both cataracts and glaucoma. Cataract formation correlates well with daily dosage and prednisolone-induced cataracts can be seen in most patients receiving 15 mg prednisolone daily. Topical application of steroids causes glaucoma by

decreasing the aqueous humour outflow. The rise in IOP is related to the anti-inflammatory strength of the steroid used and the genetic disposition of the individual.

FURTHER READING

(A full reading list is available online at <https://expertconsult.inkling.com/>).

FURTHER READING

- Cochrane, S., Dick, A.D., 2007. Tumor necrosis factor alpha-targeted therapies in uveitis. In: Pleyer, U., Foster, C.S. (Eds.), *Essentials in ophthalmology. Uveitis and immunological disorders*, Springer, Berlin-Heidelberg, pp. 177–192.
- Denton, D.M., Magee, C.C., Sayegh, M.H., 1999. Immunosuppressive strategies in transplantation, *Lancet* 353, 1084.
- Gaudana, R., Ananthula, H.K., Parenky, A., Mitra, A.K., 2010. Ocular drug delivery. *AAPS J.* 12, 348–360.
- Ingelman-Sundberg, M., 2004. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past present and future. *Trends Pharmacol Sci.* 25, 193–200.
- McGhee, C.N.J., 1992. Pharmacokinetics of ophthalmic corticosteroids. *Br. J. Ophthalmol.* 76, 681–684.