LIPID AS A DRUG TARGET

Drugs acting on cell membrane lipids - Anaesthetics and some antibiotics

Action of amphotericin B (antifungal agent)

- **builds tunnels through membrane and drains cell**

Amphotericin B is an antifungal drug often used intravenously for serious systemic fungal infections and is the only effective treatment for some fungal infections.

Common side effects include a reaction of fever, shaking chills, headaches and low blood pressure soon after it is infused, as well as kidney and electrolyte problems. Allergic symptoms including anaphylaxis may occur.

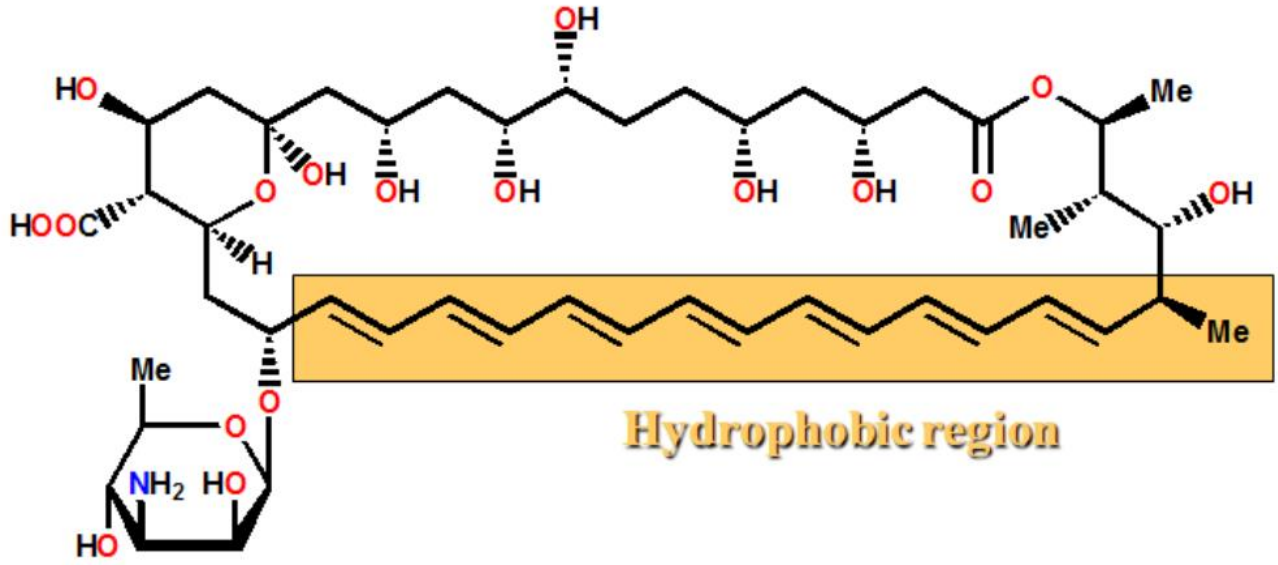
It was originally extracted from *Streptomyces nodosus*, a filamentous bacterium, in 1955, at the Squibb Institute for Medical Research. Its name originates from the chemical's amphoteric properties. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system

Mechanism of action

As with other polyene antifungals, amphotericin B binds with ergosterol, a component of fungal cell membranes, forming a transmembrane channel that leads to monovalent ion (K^+, Na^+, H^+ and Cl^-) leakage, which is the primary effect leading to fungal cell death. Researchers have found evidence that pore formation is not the only mechanism responsible for cell death.[33][34] By an unknown mechanism, amphotericin B also causes oxidative stress within the fungal cell and the addition of free radical scavengers or induction of antioxidant enzymes in pathogens can lead to amphotericin resistance in species such as scedosporium prolificans without having to effect cell wall ergosterol.

Two amphotericins, amphotericin A and amphotericin B, are known, but only B is used clinically, because it is significantly more active *in vivo*. Amphotericin A is almost identical to amphotericin B (having a double C=C bond between the 27th and 28th carbons), but has little antifungal activity.

Fig 1 -Structure of **amphotericin B**



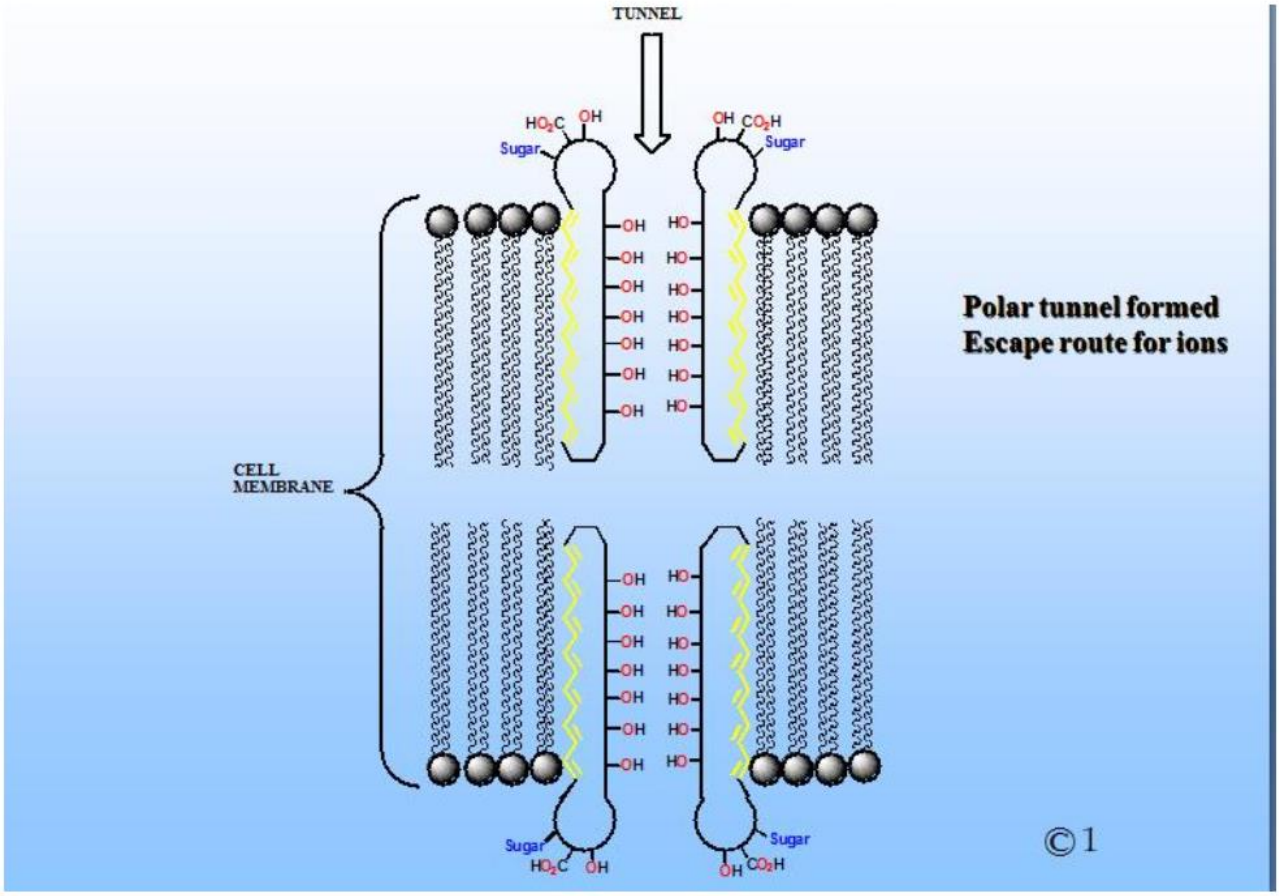
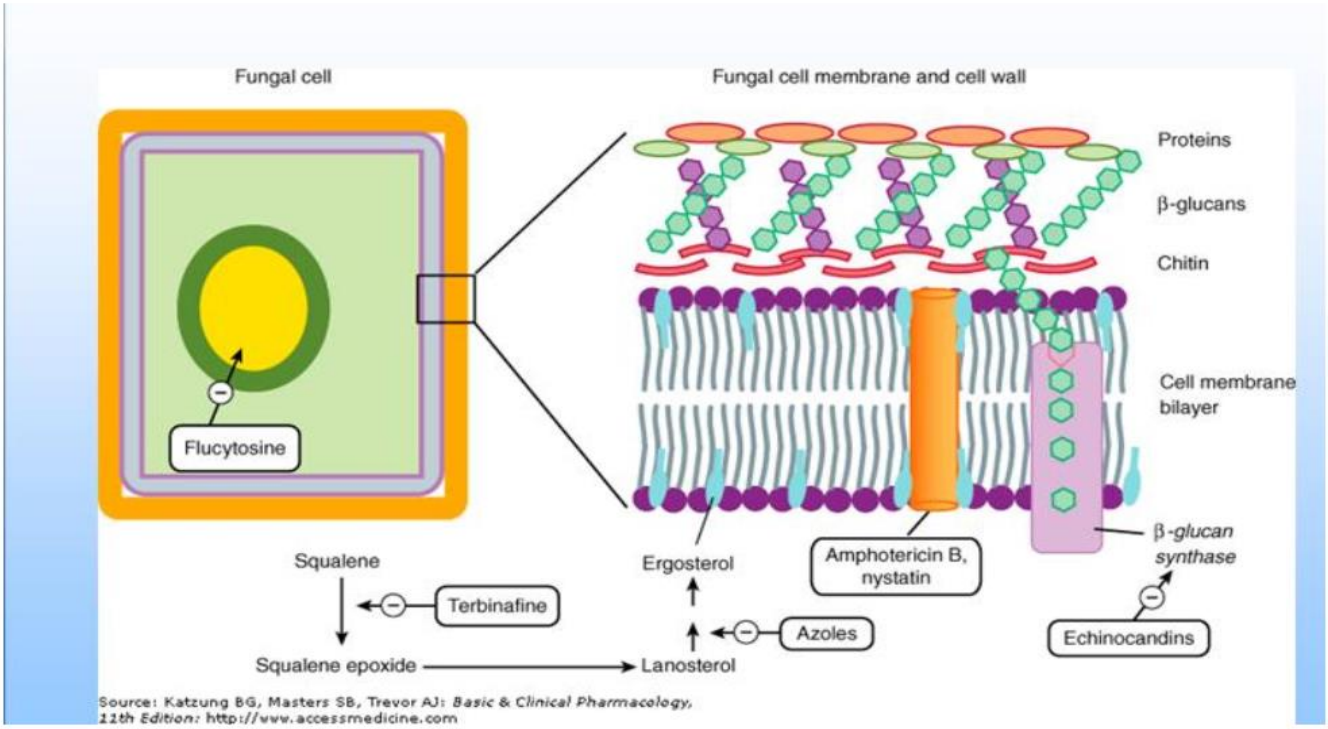


Fig 2 – structure of **amphotericin B bound** cell membrae

Fugal drug target



ION CHANNEL AS DRUG TARGET

Local Anaesthetics

Koller introduced the ester cocaine into clinical practice for eye surgery in 1884 because the conditions provided by general anaesthesia were poor. It is interesting that the use of local anaesthesia for eye surgery has once more become very popular, although much safer drugs than cocaine are now employed. In 1948 Gordh was the first to use the amide drug, lignocaine; the amide local anaesthetics are used now in preference to the esters in the U.K. as they have fewer undesirable effects. Local anaesthetics are either aminoesters (e.g. procaine) or aminoamides (e.g. lignocaine) which reversibly inhibit nerve conduction.

Mechanisms of action

Local anaesthetics inhibit nerve conduction by interfering with the physiological changes in ionic permeability during an action potential. Nerve cells are selective in their permeability to ions and consequently have an electrical potential across their membrane; at rest this is of the order of minus 50 to minus 80 mV, with the inside being negative. Cell membranes are composed mainly of lipids and do not permit ions to pass through them, but they are crossed by specialised protein ion channels, which allow potassium, sodium and other ions to pass through.

At rest, the potassium channels in nerve cell membranes are open and the sodium gates are closed; when a nerve cell is excited, the membrane suddenly becomes transiently permeable to sodium as that ionic channel opens. The membrane potential is reversed so that it has a positive charge inside, and a propagated action potential is passed along the fibre. Local anaesthetics block sodium channels, prevent the evolution of the action potential and so prevent or decrease sensation arising in the affected area. It is thought that most local anaesthetics work by blocking the sodium channel from the inside of the cell into which they must first diffuse before they can act. In infected tissues, acidic conditions prevent this diffusion and thus local anaesthetics then tend to be less effective.

Pain Management

Local anaesthetics are used on their own and combination with opioids for epidural and spinal blocks. Local anaesthetics are also used for local blocks and are used extensively for day case surgery, limb surgery and hand surgery. Local anaesthetics can also be used

systemically for pain management. Sodium channel blockers can be used to reduce pain due to nerve damage and intravenous lignocaine and oral mexiletine (an oral analogue) can both reduce neuropathic pain in nonmalignant and cancer pain

Side effects/complications

Adverse effects to local anaesthetics can be due to the use of excessive doses, abnormal reactions to normal doses, or to toxicity or depression of vital centres after inadvertent injection into the bloodstream or the cerebrospinal fluid. Toxic reactions to local anaesthetics can be reduced by slow administration, and intravenous access should always be secured before a block is performed in case of untoward events occurring. Resuscitation equipment and drugs should be immediately available. The effects of local anaesthetics are as follows:

- Central nervous system - is particularly sensitive to the effects of local anaesthetics and with increasing blood concentrations predictable consequences present. Early signs of toxicity are shivering, confusion, and twitching and tremors followed by generalised seizures. Eventually, with large doses, generalised central nervous system depression ensues with cessation of seizures, respiratory arrest and hypoxia. Treatment comprises the administration of anticonvulsants (thiopentone or diazepam) and oxygenation, with tracheal intubation and respiratory support if necessary.
- Cardiovascular system - is more resistant to local anaesthetics, but vasodilatation, myocardial depression and disorders of rhythm occur and can lead to cardiac arrest and circulatory collapse. Cardiovascular toxicity may be precipitated and worsened by hypoxia, hypercarbia and acidosis consequent to inadequate treatment of the convulsions and respiratory arrest described above. In particular, hypoxia and acidosis potentiate the cardiodepressant effects and arrhythmias associated with bupivacaine toxicity. Cardiac massage, ventricular defibrillation, intravenous fluids and inotropic support are indicated and resuscitation may be prolonged, especially with bupivacaine.
- Allergic reactions - to local anaesthetics are rare and most involve the aminoesters. There is also cross-sensitivity between the para-aminobenzoic acid derivatives and methylparaben, a preservative commonly used in local anaesthetic preparations. Allergy to amide local anaesthetics is rare, and almost all have been related to methylparaben.
- Methaemoglobin - The administration of large doses of prilocaine (10 mg/kg) may lead to the accumulation of an oxidising agent, which converts haemoglobin to methaemoglobin. Patients may appear cyanosed at a methaemoglobin concentration

of 3 - 5 g/100 ml of blood, but in healthy individuals this should not present a problem. In patients who have other cardiorespiratory abnormalities, immediate treatment for methaemoglobinaemia may be required and the reducing agent methylene blue, 1 - 5 mg/kg, should be given intravenously. Lignocaine also produces methaemoglobin, but a clinical problem rarely presents. Prilocaine may be a problem if EMLA is used in large quantities on premature babies.

Specific drugs

Lignocaine

This is the most commonly used agent in the U.K.; it is available in solutions of 0.5 - 2%. The effect of lignocaine is prolonged considerably by the addition of the vasoconstrictor adrenaline.

Bupivacaine

Bupivacaine is more potent than lignocaine; 0.5% bupivacaine is as effective as 2% lignocaine. It is available in 0.25 - 0.75% concentrations. It is more cardiotoxic than other local anaesthetics and is not recommended for intravenous regional analgesia. The duration of action is from 4 to 16 hours, and bupivacaine produces more sensory than motor block. Levo-bupivacaine is also available and while the concentrations and usage are the same as bupivacaine, evidence suggests that it may be less cardiotoxic.

Prilocaine

The potency of prilocaine is similar to lignocaine but as it is metabolised in the lung as well as the liver it is cleared from the body more quickly than the other amides (this makes it particularly useful for intravenous regional analgesia). Methaemoglobinaemia is associated with the use of high doses and it is unsuitable for use in obstetrics because of this risk to the unborn child.

Ropivacaine

Ropivacaine is a long acting local anaesthetics like bupivacaine but is associated with less cardiovascular toxicity. It is one of the newer local anaesthetics

ENZYME AS DRUG TARGET

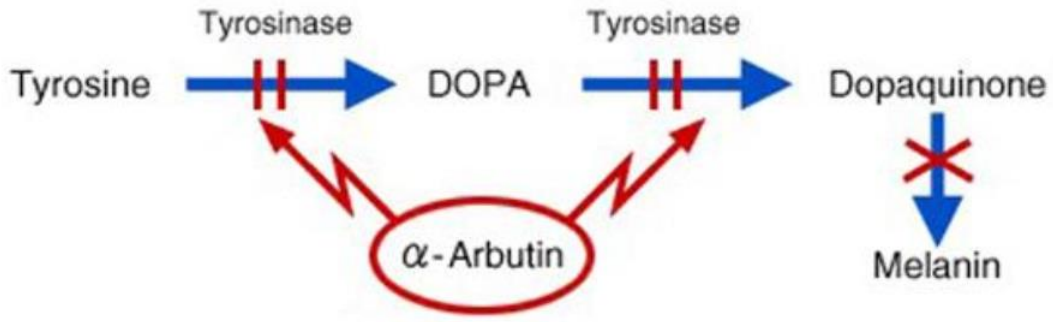
Drug – arutin

Arbutin

- Arbutin is one of the most widely prescribed skin-lightening and de-pigmenting agent worldwide.
- Arbutin, the b-D-glucopyranoside derivative of hydroquinone, is a naturally occurring plant derived compound found in dried leaves of a number of different plant species including, bearberry, blueberry, cranberry and pear trees.
- Arbutin, inhibits tyrosinase activity competitively but at non-cytotoxic concentrations in a dose dependent manner in cultured melanocytes.
- It also inhibits melanosome maturation and is less cytotoxic to melanocytes than hydroquinone.
- Although, higher concentrations may be more efficacious, greater risk for paradoxical hyperpigmentation exists.
- Controlled trials on treating hyperpigmentation are lacking.

How alpha arbutin works

Arbutin inhibits the formation of melanin pigment by inhibiting Tyrosinase activity.



PENICILLINS- EXAMPLE FOR ENZYME AS DRUG TARGET

Bacteria constantly remodel their peptidoglycan cell walls, simultaneously building and breaking down portions of the cell wall as they grow and divide.*β*-Lactam antibiotics inhibit the formation of peptidoglycan cross-links in the bacterial cell wall; this is achieved through binding of the four-membered *β*-lactam ring of penicillin to the enzyme DD-transpeptidase. As a consequence, DD-transpeptidase cannot catalyze formation of these cross-links, and an imbalance between cell wall production and degradation develops, causing the cell to rapidly die.

The enzymes that hydrolyze the peptidoglycan cross-links continue to function, even while those that form such cross-links do not. This weakens the cell wall of the bacterium, and osmotic pressure becomes increasingly uncompensated—eventually causing cell death (cytolysis). In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the cell wall's peptidoglycans. The small size of the penicillins increases their potency, by allowing them to penetrate the entire depth of the cell wall. This is in contrast to the glycopeptide antibiotics vancomycin and teicoplanin, which are both much larger than the penicillins

Gram-positive bacteria are called protoplasts when they lose their cell walls. Gram-negative bacteria do not lose their cell walls completely and are called spheroplasts after treatment with penicillin.

Penicillin shows a synergistic effect with aminoglycosides, since the inhibition of peptidoglycan synthesis allows aminoglycosides to penetrate the bacterial cell wall more easily, allowing their disruption of bacterial protein synthesis within the cell. This results in a lowered MBC for susceptible organisms.

Penicillins, like other *β*-lactam antibiotics, block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, thephotosynthetic organelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This supports the endosymbiotic theory of the evolution of plastid division in land plants.

The chemical structure of penicillin is triggered with a very precise, pH-dependent directed mechanism, effected by a unique spatial assembly of molecular components, which can activate by protonation. It can travel through bodily fluids, targeting and inactivating enzymes responsible for cell-wall synthesis in gram-positive bacteria, meanwhile avoiding the surrounding non-targets. Penicillin can protect itself from spontaneous hydrolysis in the body in its anionic form, while storing its potential as a strong acylating agent, activated only upon approach to the target transpeptidase enzyme and protonated in the active centre. This targeted protonation neutralizes the carboxylic acid moiety, which is weakening of the β-lactam ring N–C(=O) bond, resulting in a self-activation. Specific structural requirements are equated to constructing the perfect mouse trap for catching targeted prey.

DNA AS DRUG TARGET

Ex- Doxorubicin

Mechanism of action

Diagram of two doxorubicin molecules intercalating DNA, from PDB:1D12

Doxorubicin interacts with DNA by intercalation and inhibition of macromolecular biosynthesis. This inhibits the progression of the enzyme topoisomerase II, which relaxes supercoils in DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process ofreplication. It may also increase quinone type free radical production, hence contributing to its cytotoxicity.

The planar aromatic chromophore portion of the molecule intercalates between two base pairs of the DNA, while the six-membered daunosamine sugar sits in the minor groove and interacts with flanking base pairs immediately adjacent to the intercalation site, as evidenced by several crystal structures.

By intercalation, doxorubicin can also induce histone eviction from transcriptionally active chromatin. As a result, DNA damage response, epigenome and transcriptome are deregulated in doxorubicin-exposed cells.

PROTEIN AS DRUG TARGET

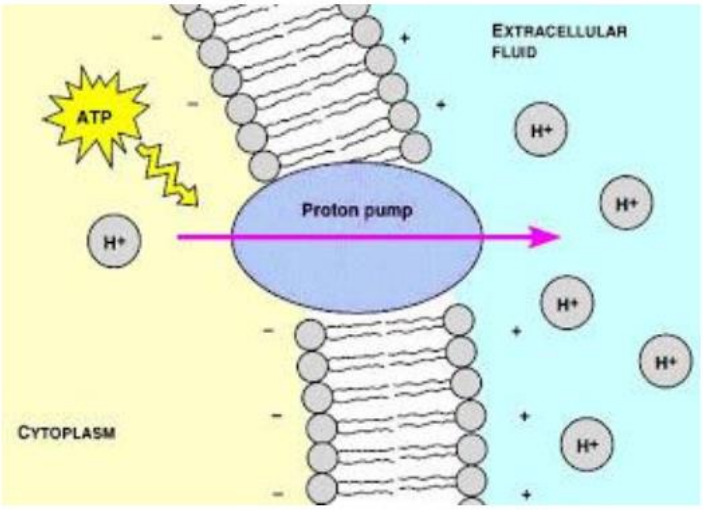
Omeprazole, sold under the brand names **Prilosec** and **Losec** among others, is a medication used to treat gastroesophageal reflux disease, peptic ulcer disease, and Zollinger–Ellison syndrome. It is also used to prevent upper gastrointestinal bleeding in people who are at high risk It is taken by mouth.

Mechanism of action[edit]

Omeprazole is a selective and irreversible proton pump inhibitor. It suppresses stomach acid secretion by specific inhibition of the H^+/K^+-ATPase system found at the secretory surface of gastric parietal cells. Because this enzyme system is regarded as the acid (proton, or H^+) pump within the gastric mucosa, omeprazole inhibits the final step of acid production.

Omeprazole also inhibits both basal and stimulated acid secretion irrespective of the stimulus.

fig 1- **proton pump**



A **proton pump** is an integral membrane protein that is capable of moving **protons**across a biological membrane. Mechanisms are based on conformational changes of the protein structure or on the Q cycle.