St Peter's Institute of Pharmaceutical Sciences

Course : Bachelor of Pharmacy

Subject : Medicinal Chemistry I

Subject Code: BP402T

Introduction to Medicinal Chemistry

What is medicinal chemistry? • The science that deals with the discovery or design of new therapeutic chemicals and the development of these chemicals into useful medicine.

What is "medicine"? Drugs, pharmaceutics, Media distinction between drugs that are used in medicine and drugs that are abused (addiction). A compound that interacts with a biological system, and produces a biological response (ideally desired and positive)

"Good" vs. "Bad" Drugs. No medicine has only benefits or drawbacks.A "good" medicine would have to satisfy the following criteria, it would have to do what it is meant to do and have no toxic or unwanted side effects and be easy to take. For example, Morphine in low dose it is an Excellent analgesic, but have serious side effects such as, Addiction, tolerance (the effect of the drug diminishes after repeated doses and so we need to increase the size of the dose to achieve the same results.), Respiratory depression and it may kill if taken in excess. There is a long history of plants being used to treat various diseases.

Basically, the subject of medicinal chemistry explains the design and production of compounds that can be used for the prevention, treatment or cure of human and animal diseases. Medicinal chemistry includes the study of already existing drugs, of their biological properties and their structure-activity relationships. Medicinal chemistry was defined by IUPAC specified commission as "it concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level".

Medicinal chemistry covers the following stages:

(i) In the first stage new active substances or drugs are identified and prepared from natural sources, organic chemical reactions or

biotechnological processes. They are known as lead molecules.

(ii) The second stage is optimization of lead structure to improve potency, selectivity and to reduce toxicity.

(iii) Third stage is development stage, which involves optimization of synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substance to render it clinically useful.

Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants. Today, scientists in this field are also equally concerned with the creation of new synthetic compounds as drugs. Medicinal chemistry is almost always geared toward drug discovery and development. Medicinal chemists apply their chemistry training to the process of synthesizing new pharmaceuticals. They also work on improving the process by which other pharmaceuticals are made. Most chemists work with a team of scientists from different disciplines, including biologists, toxicologists, pharmacologists, theoretical chemists, microbiologists, and biopharmacists. Together this team uses sophisticated analytical techniques to synthesize and test new drug products and to develop the most cost-effective and eco-friendly means of production.

History and Development of Medicinal Chemistry

In the Middle Ages various 'MateriaMedica and pharmacopeas brought together traditional uses of plants. The herbals of John Gerard (1596), John Parkinson (1640) and Nicolas Culpeper (1649) provide an insight into this widespread use of herbs. Exploration in the seventeenth and eighteenth centuries led to the addition of a number of useful tropical plants to those of European origin.

The nineteenth century saw the beginnings of modern organic chemistry and consequently of medicinal chemistry. Their development is intertwined. The isolation of a number of alkaloids including morphine (1805), quinine (1823) and atropine (1834) from crude medicinal plant extracts was part of the analytical effort to standardize drug preparations and overcome fraud. General anaesthetics were introduced in surgery from 1842 onwards (diethyl ether (1842), nitrous oxide (1845) and chloroform (1847)). Antiseptics such as iodine (1839) and phenol (1860) also made an important contribution to the success of surgery. The hypnotic activity of chloral (trichloroethanal) (1869) was also reported. Many of the developments after the 1860s arose from the synthesis of compounds specifically for their medicinal action. Although the use of willow bark as a pain-killer was known to the herbalists, the analgesic activity of its constituent salicin and of salicylic acid were developed in the 1860s and 1870s. p-Hydroxyacetanilide (paracetamol) and phenacetin (1886) were also recognized as pain-killers. Acetylation of salicylic acid to reduce its deleterious effect on the stomach led to the introduction of aspirin in 1899. However its mode of action was not established until 1971.The local anaesthetic action of cocaine was reported in 1884 although its structure was not known at the time.Various modifications of the dialkylamino esters of aromatic acids modelled on part of the structure of cocaine led to benzocaine (1892) and procaine (1905). The barbiturates, veronal (1903) and phenobarbital (1911) were introduced as sleeping tablets. The action of acetylcholine on nerve tissue had been recognized in the late nineteenth century. Barger and Dale (1910) examined the response of various tissues to acetylcholine agonists and showed that there were different receptor sub-types; some responding to muscarine and others to nicotine.

The 1920s and 1930s saw the recognition of vitamin deficiency diseases and the elucidation of the structure of various vitamins. It was also a period in which

there was exposure of many Europeans to tropical diseases. The iodinated quinolines such as entero-vioform were introduced to combat amoebic dysentary and complex dyestuff derivatives such as suramin and germanin were developed in the 1920s to treat sleeping sickness. Synthetic anti-malarials such as pamaquine (1926), mepacrine (1932) and later chloroquine (1943) and paludrine (1946) were introduced as quinine replacements. In 1935 Domagk observed the anti-bacterial action of the sulfonamide dyestuff, prontosil red, from which the important family of sulfonamide anti-bacterial agents were developed. The activity of these compounds as inhibitors of folic acid biosynthesis was rationalized by Woods (1940) as anti-metabolites of p-aminobenzoic acid. With the onset of the Second World War, there was a need for new antibiotics. In 1929 Fleming had observed that a strain of Penicilliumnotatum inhibited the growth of a Staphylococcus. In 1940-1941 Chain, Florey and Heaton isolated benzylpenicillin. After considerable chemical work, the b-lactam structure for the penicillins was established. The relatively easy bio-assays for anti-bacterial and anti-fungal activity led to the isolation of a number of antibiotics including streptomycin (1944), chloramphenicol (1949) and the tetracyclinessuch as aureomycin (1949). Several different aspects of medicinal chemistry developed in parallel through the second half of the twentieth century. Although they did not develop independantly, it is easier to follow their progression by considering them separately. The structures of the steroid hormones were established in the 1930s and 1940s. The discovery in 1949 of the beneficial effect of cortisone in alleviating the inflammation associated with rheumatism provided the stimulus for synthetic activity in this area. A number of anti-inflammatory semi-synthetic corticosteroids such as prednisolone, betamethasone and triamcinolone became available in the late 1950s and 1960s.A number of developments took place in the 1960s, which changed medicinal chemistry. It was found that a drug, thalidomide , which had been introduced as a sedative, when used by pregnant women, led to the birth of deformed children. The consequences of this teratogenic effect brought about a major tightening of the regulations regarding drug registration and the safety of medicines. Unfortunately there was some tardiness in the recognition of this side-effect. Second in 1964 Hansch published correlations between substituent effects (Hammett parameters) and the biological activity of some aromaticcompounds. These QSAR began to provide a framework for the

systematic development of drugs and for decisions to be made in the planning of a research programme.

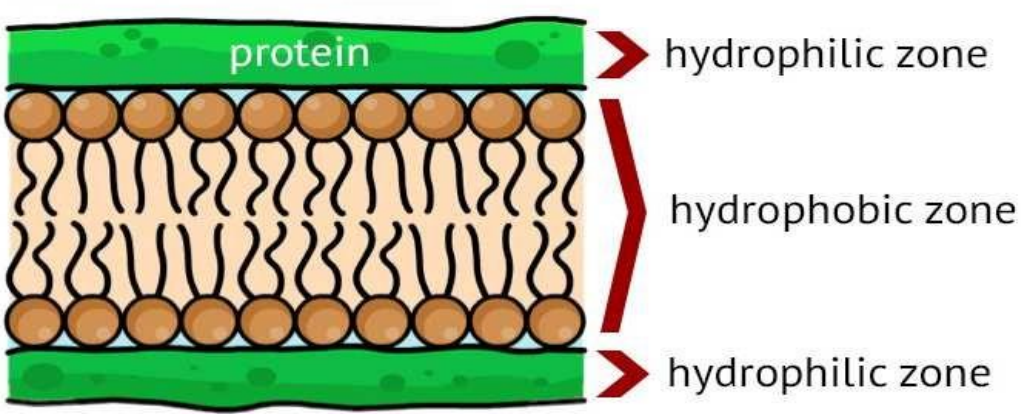
The logical development during the 1960s of histamine antagonists for the treatment of peptic ulcers led to cimetidine (1976) and then ranitidine (1981). The reasoning behind this work had a major impact on the development of medicinal chemistry. Paul Ehrlich was such a scientist who got fascinated by the ability of colourful dyes to interact with cellular and histological structures. He procured hundreds to thousands of dyes for his research from several chemical companies for several decades. Ehrlich found that the biological effect of a chemical compound depends on its chemical composition and the cell on which it acts. He established a connection between chemistry, biology, and medicines in a creative way. He was also inspired by his colleagues who were conducting researches in immunology including Louis Pasteur, Robert Koch, Emil Von Behring, and Shibasaburo Kitasato. In the 20th century, Ehrlich came up with the receptor theory; and this theory became influential to make understand how drugs bind to receptors based on their chemical structures and compositions.

Structure of Biological Membrane

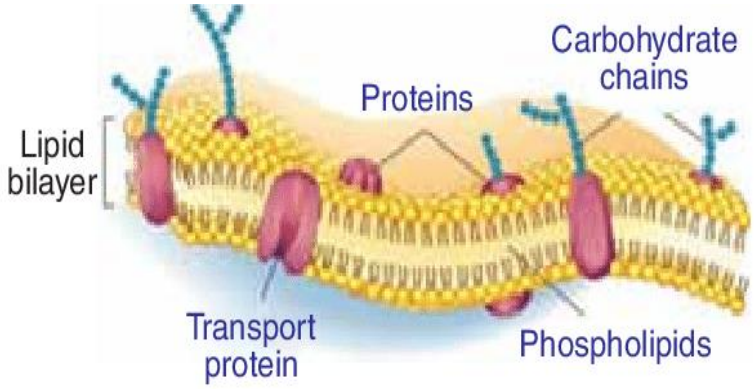
Biological Membrane (or cell membrane, plasma membrane, and plasma membrane) is a selectively permeable membrane which allows only certain substances to pass through it, and also acts as a barrier between the inner and outer surface of the cell. Celt membrane comprises of lipids and proteins along with other living molecules, which participate in the normal functioning of cells such as cell signalling, ion channel conductance, and cell adhesion. The inner cytoskeleton of the cell connects to its outer cell wall via cell membrane. Cell membrane defines the external boundaries of the cells and regulates traffic of molecule across the boundary. In eukaryotic cells, cell membrane divides the internal space into discrete compartments to segregate processes and components. It regulates the sequences of complex biochemical reactions and participates m conservation of biological energy and participates in cell-to-cell communication.

Models Depicting Structure of Cell Membrane

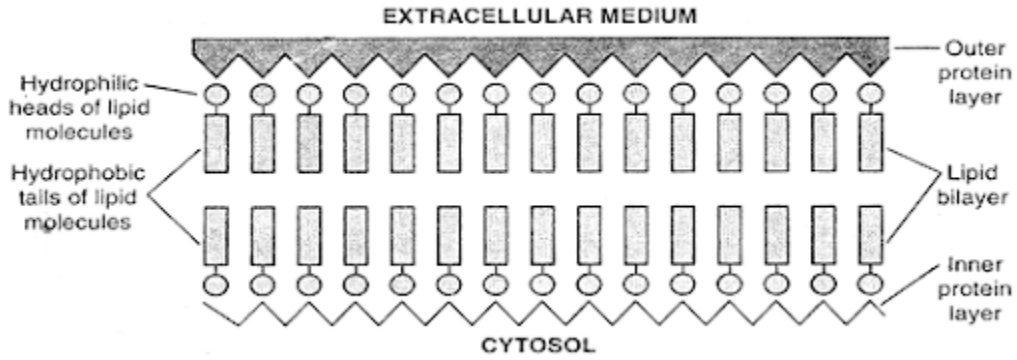
l**. Danielli and Davson Model:** Danielli and Davson (early 1930s-40s) have given the Lamellar theory in which they studied the arrangement of triglyceride lipid bilayer on the water surface. This model States that the plasma membrane has bimolecular phospholipids made up of two protein layers present as folded ß-chains. By electrostatic bond, these protein molecules are attached to the lipid at polar hydrophilic ends.



2. Unit Membrane Model: According to this model, cell membrane is a continuous structure having cytoplasm on one side and extra cellular fluid on the other. Under the electron microscope, it appears as a thin, triple-layered structure with 7.5- 10 nm thickness. The membrane has two parallel dense strata each with 2.5nm thickness; these strata are separated by a light inter- zone of nearly same thickness. Isolated vesicles are formed in the cell by the folding of plasma membrane into the cytoplasm; these vesicles store extracellular material by endocytosis process.



3. on's Model: Through an electron microscope. Robertson revealed the tri-laminar structure of biological membrane. He observed two parallel dark hydrophili layers (of 20-25Å width) and a middle light hydrophobic layer (of 25-35Å width) comprising the biological membrane. Organelles like nucleus, mitochondria. endoplasmic reticulum etc. also have same tri-laminar membrane. Robertson stated that biological membrane is composed of bimolecular lipid layers sandwiched between outer and protein-layers.



4. The Fluid mosaic model– It was first proposed by S.J. Singer and Garth L. Nicolson in 1972 to explain the structure of the plasma membrane. The model has evolved somewhat over time, but it still best accounts for the structure and functions of the plasma membrane as we now understand them. The fluid mosaic model describes the structure of the plasma membrane as a mosaic of components including phospholipids, cholesterol, proteins, and carbohydrates that gives the membrane a fluid character. Plasma membranes range from 5 to 10 nm in thickness. For comparison, human red blood cells, visible via light microscopy, are approximately 8 µm wide, or approximately 1,000 times wider than a plasma membrane. The proportions of proteins, lipids, and carbohydrates in the plasma membrane vary with cell type. For example, myelin contains 18% protein and 76% lipid. The mitochondrial inner membrane contains 76% protein and 24% lipid. The main fabric of the membrane is composed of amphiphilic or dual-loving, phospholipid molecules. The hydrophilic or water-loving areas of these molecules are in contact with the aqueous fluid both inside and outside the cell. Hydrophobic, or water-hating molecules, tend to be non- polar. A phospholipid molecule consists of a three-carbon glycerol backbone with two fatty acid molecules attached to carbons 1 and 2, and a phosphate-containing group attached to the third carbon. This arrangement gives the overall molecule an area described as its head (the phosphate-containing group), which has a

polar character or negative charge, and an area called the tail (the fatty acids), which has no charge

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4. Introduction to principles of drug design- Smith and Williams.
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6. Martindale's extra pharmacopoeia