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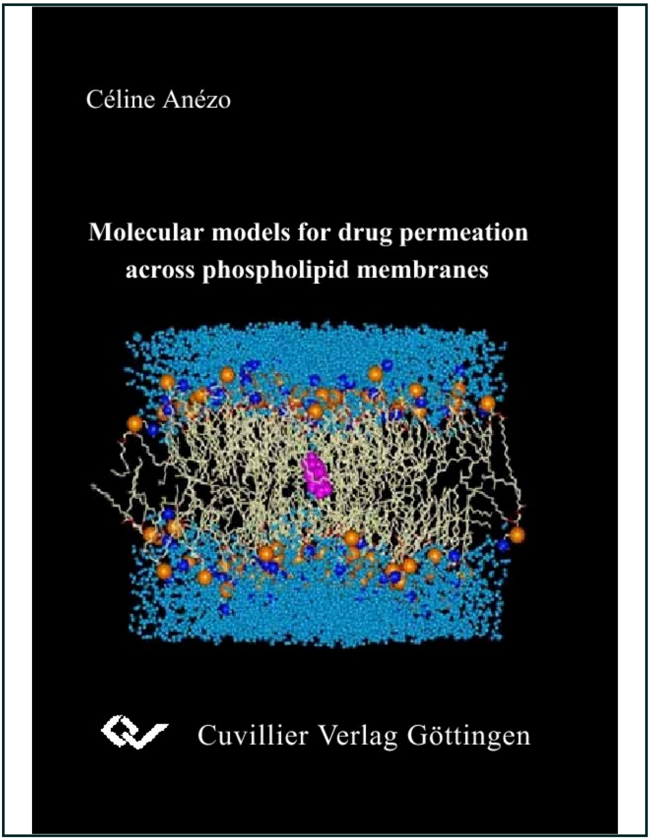
Molecular models for drug permeation across phospholipid membranes



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Chapter 1

Introduction

In 1884, Thudichum already stated: “Phospholipids are the centre, life, and chemical soul of all bioplasm whatsoever, that of plants as well as animals” [1]. If the fluid lipid bilayer, representing the core of the membrane, is now well established as the fundamental structure of most biomembranes, it took however a long time to really appreciate the role of lipids in membrane structure and function and to realize the importance of solute-lipid interactions in membranes for cell functioning.

This introductory chapter presents first the main features of biomembranes, underlines then properties of phospholipids relevant to biomembranes, and focuses finally on transport processes across biomembranes and, more precisely, on drug absorption.

1.1 Biomembranes

1.1.1 Organization, structure, and functions

1.1.1.1 Organization

Each biological cell is enclosed by its outer plasma membrane which provides a barrier between intracellular and extracellular domains and controls interactions between the cell and its surroundings. This description applies both to the relatively small prokaryotic cells, which have no cell nucleus, and to the much larger eukaryotic cells, which do have such a nucleus. Bacteria have prokaryotic cells, while animals, plants, as well as single-celled microorganisms such as yeasts have eukaryotic cells.

Prokaryotic cells Prokaryotes exhibit the most simple organization of cell membranes, containing no nucleus and no organelles. The plasma membrane determines the boundary of the cytoplasm and forms a semipermeable barrier between the intracellular and extracellular environments. Some prokaryotes possess an extracellular matrix. The plasma membrane is then surrounded by a cell wall, which is not a membrane and represents a relatively rigid structure held together essentially by covalent forces. Outside the cell wall of bacteria is the outer membrane of the cell. Its structure is not as rigid as that of the cell wall, but its composition differs from that of the plasma membrane.

Eukaryotic cells The organization of nucleated cells is more complex. In addition to the plasma membrane, eukaryotic cells contain an impressive array of cytoplasmic organelles, each surrounded by its own membrane. These intracellular compartments ensure various cellular activities and allow more diverse and specialized functions than are possible in prokaryotic cells. To the internal organelles belongs the nucleus, the endoplasmic reticulum (ER), Golgi complexes, mitochondria, lysosomes, and chloroplasts. Their functional specialization arises from distinctive characteristics of their membranes: each of these organelle membranes exhibits a unique lipid and protein composition, which is directly related to a typical function. In the case of plant cells, the plasma membrane may in addition be surrounded by a cell wall.

1.1.1.2 Structure

On the molecular level, biological membranes are quite complex: they are composed of specific mixtures of lipids and proteins, which account for their diverse functions. Despite their complex composition, all biomembranes exhibit a universal construction principle. They essentially consist of a two-dimensional matrix made up of a lipid bilayer, interrupted and coated by proteins. The hydrocarbon chains of the lipids confer a hydrophobic character on the membrane interior, whereas the polar headgroups found in the interfacial region have hydrophilic properties. This structural pattern results directly from the so-called *hydrophobic effect* (see Section 1.2.1, page 28, for more details), whereby the apolar lipid chains and the hydrophobic side-chains of amino acid residues in proteins tend to minimize contacts with the aqueous phase. Figure 1.1 provides a simplified but informative picture of membrane structure.

The components of the bilayer matrix are held together largely by non-covalent forces. Thus, biomembranes are not rigid structures, but are rather deformable. The hydrophobic effect accounts for most of the interaction energy that stabilizes the bilayer organization. Hydrogen bonding and electrostatic interactions, however, contribute significantly to the consolidation of this assembly in the interfacial region, while dispersive forces between the lipid hydrocarbon chains stabilize the core of the membrane.

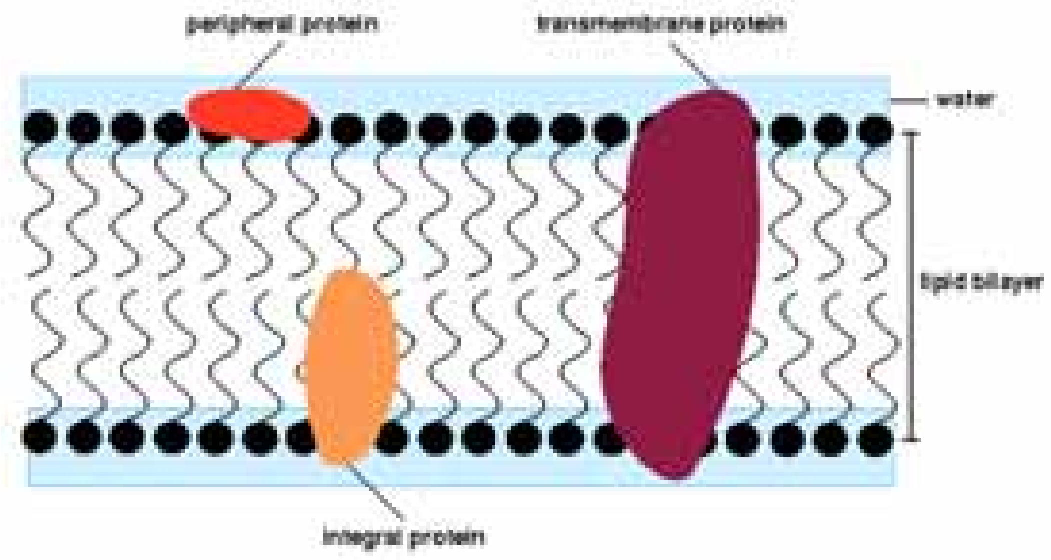

Figure 1.1: Schematic representation of a typical biomembrane.

1.1.1.3 Functions

Even though each membrane exhibits functions unique to that membrane, general functions, common to all membranes, can be distinguished.

The first basic function of biomembranes is to provide different spatial compartments in living organisms. Compartmentalization, *i.e.* the physical separation of one compartment from another, supplies morphological identity to the cell and its organelles.

Biomembranes act as selective barriers for the exchange of molecules between the different compartments, and ultimately, protect the internal microenvironments from the variability and fluctuations of their surroundings. They sustain concentration gradients of chemical species from one side to the other and the cell makes use of the membrane to create, maintain, or utilize the energy stored in these concentration gradients.

The bilayer matrix provides a two-dimensional network in which various functional molecules such as enzymes are specifically distributed and oriented. Lipids act not only as solvent but also as anchors, activators, and conformational stabilizers for proteins which carry out specific catalytic and translocation functions.

Another important aspect is the transduction of molecular information across and along membranes. For instance, receptors located on the cell surface receive extracellular signals that are conveyed to the cell interior which alters its behavior in response.

The plasma membrane defines the cell boundary and delineates intracellular from extracellular domains. This outer membrane plays an important regulatory role in the metabolism of the cell, controlling the entrance and exit of solutes. Due to these protective functions, the plasma membrane constitutes a fundamental ingredient for life: cell components could not probably survive without the enclosure by a membrane. The plasma membrane together with the cytoskeleton is responsible for the unique combination of flexibility and mechanical stability of cells. In the plasma membrane are also embedded various proteins which fulfill a great number of vital functions such as energy-driven transport of ions and metabolites, receptor-mediated events, synthesis of membrane components, secretion, ATP synthesis... Another function of the plasma membrane is to control cell-cell interactions. During their development, cells differentiate and organize into tissues. In this process, cells have to recognize the right matrix and aggregate together according to the pattern dictated by their genome. Cell-cell and cell-matrix recognition processes are mediated by the plasma membrane through receptors [2].

The intracellular membranes found in eukaryotic cells not only enclose the different organelles but are also involved in a series of cellular processes such as biosynthesis, transport, recycling, energy metabolism, and degradation.

1.1.2 Composition

The major components of membranes are lipids and proteins. Depending on the type of membrane, their relative amounts vary significantly, ranging from about 20% protein (dry weight) in myelin to 80% protein in mitochondria.

1.1.2.1 Membrane lipids

The most striking feature of membrane lipids is their very large diversity. Considering the possible number of structural and conformational lipid isomers, a hundred of components is involved in eukaryotic cells. In spite of this diversity, only a few classes of lipids predominate in membranes of a given type of organisms. In this section, the main classes of lipids are described with regard to their molecular characteristics.

Glycerophospholipids The glycerophospholipids are the predominant phospholipids found in biological membranes. They are derivatives of glycerol phosphate and contain an asymmetric carbon atom. Two glycerol hydroxyls are linked to hydrophobic hydrocarbon chains. A stereospecific numbering (*sn*) of the glycerol carbon atoms is commonly used in the nomenclature of glycerophospholipids, as indicated in Figure 1.2. In this nomenclature, the two hydrocarbon chains can be differentiated as *sn*-1 and *sn*-2 chains, the phosphate group being usually at the *sn*-3 position of the glycerol. In biological membranes, most of the glycerophospholipids are derivatives of *sn*-glycero-3-phosphatidic acid, the R-stereoisomer. The various glycerophospholipid types depend on the organic base, amino acid, or alcohol (the X-group in Figure 1.3) to which the phosphate is esterified and on the hydrocarbon chains which can be attached to the glycerol moiety through ester or ether linkages and vary widely in terms of length, branching, or degree of unsaturation.

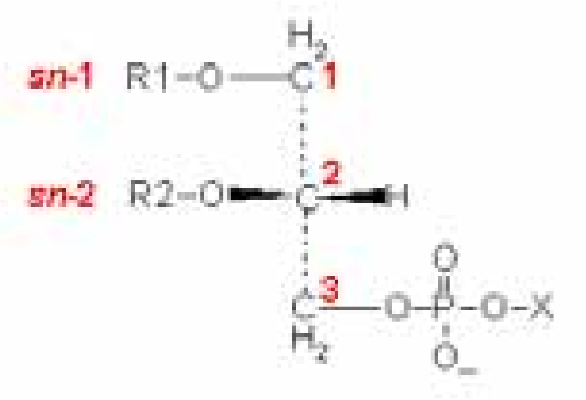

Figure 1.2: General structure of glycerophospholipids with the glycerol backbone drawn in a Fischer projection. The stereospecific numbering (*sn*) of the glycerol carbon atoms, with the distinction between the *sn*-1 and *sn*-2 chains, is indicated.

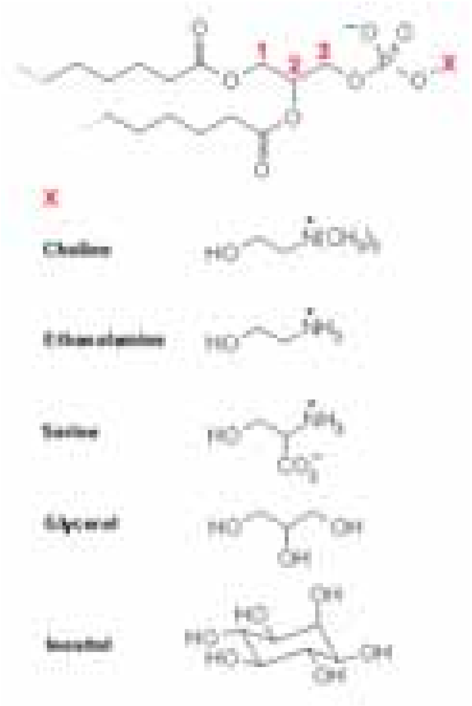

Figure 1.3: Generic structure of phospholipids. The phosphate can be esterified to the various X-groups listed to form the different classes of phospholipids.

- ***1,2-Diacylglycerophospholipids or phospholipids*** These fatty acid esters of glycerol are the predominant lipids in most biomembranes. The phosphate is usually linked to one of the several groups listed in Figure 1.3, including choline, ethanolamine, the S-amino acid serine, and polyalcohols such as glycerol or inositol. The corresponding phospholipids are called phosphatidylcholines (commonly abbreviated PC), phosphatidylethanolamines (PE), phosphatidylserines (PS), phosphatidylglycerols (PG), and phosphatidylinositols (PI). PC and PE constitute the major components of biological membranes. The chemical structure of these polar headgroups determines what charge the phospholipid as a whole may carry. At physiological pH values, PC and PE carry a full negative charge on the phosphate and a full positive charge on the quaternary ammonium: they are thus zwitterionic but electrically neutral. PS contain, in addition to the negatively charged phosphate and the positively charged amino group, a negatively charged carboxyl group. At neutral pH, PS exhibit an overall negative charge. PG and PI carry a net negative charge, since the alcoholic moiety does not carry any positive charge to counterbalance the negative charge on the phosphate. The headgroup charges are held at the interface between the aqueous and hydropho-