TRANSFER OF DRUGS ACROSS SPECIFIC MEMBRANES

An Essay Submitted in Partial Fulfillment of the Master Degree in Anaesthesiology and I.C.U.

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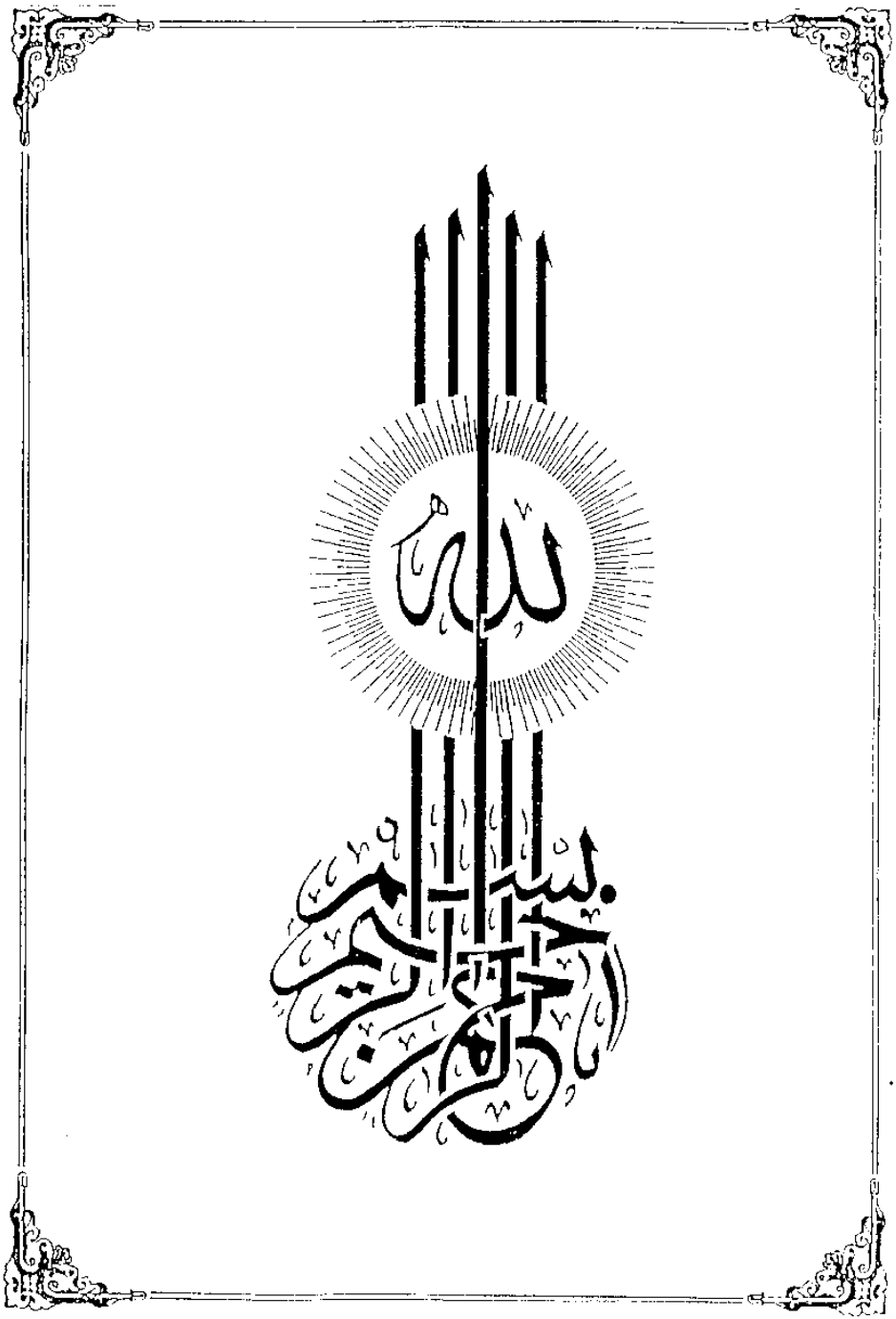

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Mohamed Attia

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TO MY FAMILY

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Introduction

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The concept of the blood-placental barrier as a modified lipid membrane is coming from the behaviour of drugs with differing degree of ionization and lipid solubility in crossing the placenta.

The anaesthetic drugs like intravenous anaesthetics, inhalational anaesthetics, narcotics, muscle relaxants, and other drugs like local anaesthetics, sedatives, antibiotics and atropine, each group differs from the other in crossing of the placenta and BBB. The drugs which will cross the BBB will differ in their cerebral effects, such as the cerebral blood flow (CBF), cerebral metabolic rate for O2 (CMRO2). the intracranial pressure (ICP) changes, and the neuroelectric effects presented by the EEG. The drugs which will cross the placenta, will differ in their effect on the fetus or newborn, and their concentration difference between maternal and fetal blood.

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Membrane Physiology

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Membrane Physiology

Biological membranes play a crucial role in almost all cellular phenomena. The plasma membrane defines the cell boundary and has important functions in communication between cells, and in cell adhesion and immunogenicity.

However, the most important function of the plasma membrane is its role as a continuous barrier around the cell which selectively limits or facilitates the passage of substances into and out of the cytoplasm. Intracellular membranes both delineate and mediate various functions of cell organelles ***(Houslay and Stanely, 1982)***.

Membrane structure:

All biological membranes, both plasma membranes and the internal membranes of eucaryotic (nucleated) cells, have a common overall morphology. The basic structure is a continuous double layer of lipid molecules, which has fluid properties and acts as a relatively impermeable barrier to water and charged molecules ***(Gorter and Grendell, 1925)***.

This bilayer is punctated with a wide variety of embedded proteins which mediate the various functions of membranes, and acts as specific receptors, enzymes and transporters. This model of membrane structure is termed the "fluid mosaic model", and is

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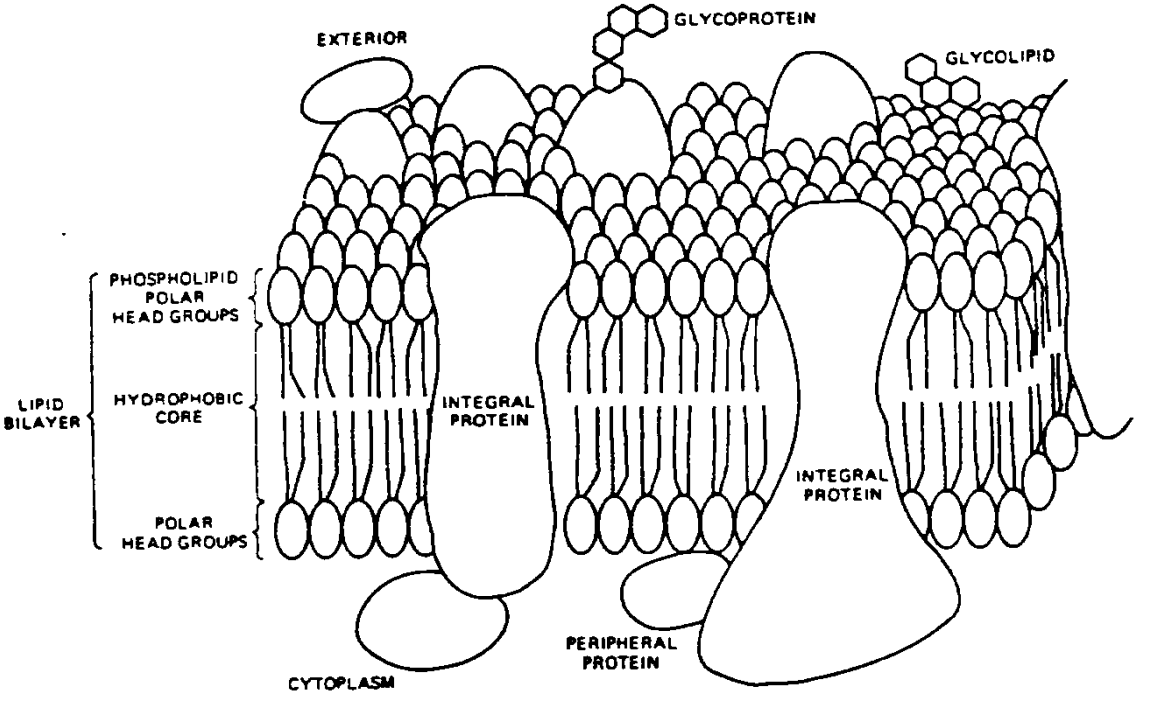

Fig. 1: Model of membrane structure. The continuous double layer of phospholipid molecules is arranged with polar headgroups at the membrane surface and the fatty acid chains meeting in the interior of the membrane. Integral proteins are embedded in the bilayer whereas peripheral proteins are loosly attached at the membrane surface. Carbohydrates group are confined exclusively to the external or normocytoplasmic membrane surface.

(From scientific foundation of anaesthesia, Felicity Hawker)

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developed from thermodynamic considerations of the various membrane components ***(Singer and Nicolson, 1972).*** (Fig.1)

Thermodynamic theory requires that the membrane adopts its lowest free energy state. In hydrophilic interactions, thermodynamic factors are responsible for the sequestering of non polar groups away from water, on the other hand, in hydrophilic interactions, thermodynamic factors dictate that ionic and polar groups prefer an aqueous rather than a non polar environment.

Both membrane lipids and membrane proteins are amphipathic i.e. their molecules have both hydrophobic and hydrophilic domains. Hence non polar amino acids residues of membrane proteins, and the fatty acid chains of phospholipids are sequestered away from water in membrane interior, while the ionic and polar groups of the proteins, lipids, and oligopolysaccharides are incontact with the aqueous environment on the peripheral face of the membrane.So with this confirmation, the intact membrane achives the lowest free energy state ***(Singer and Nicolson, 1972).***

In this model both lipids and proteins can both rotate and diffuse laterally in the plane of membrane, although lateral movement of membrane proteins may be limited to some extent by the cell cytoskeleton ***(Schlessinger, 1983).***

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Under usual circumstances for the above thermodynamic reasons, rather lipids, nor proteins transfer from the half of bilayer to the other, the cell membrane is also asymmetrical ***(Rothman and Lenard, 1977)***.

The lipid and protein components of the cytoplasmic and external faces differs in ways that reflect the different functions performed at the two surfaces ***(Rasmussen, 1986)***.

Although aspects of this model have been criticized, it provides a useful structural basis for understanding membrane transport phenomena ***(Houslay et al., 1982)***.

The thickness of the membrane is 8-10 nm. The question of whether body membranes consist of a continuous lipid barrier or a discontinuous lipid mosaic interspersed with aqueous channels or "pores" remains a controversial issue. The presence of "pores" in body membranes seems necessary to account for the ready passage of water and small lipid insoluble molecules, and ions across it. This is particularly so for the blood capillary membrane which behaves as atypical "lipid-pore" barrier, lipid soluble substances peneterate readily at a rate determined by their lipid/water partition coefficient, whilst soluble substances penetrate less readily at rates determined by molecular size and electrical charge. Such behaviour is consistent with the belief that membrane structure incorporates a system of pores, and studies of

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comparative permeability to various substances have allowed measurments to be derived of equivalent pore radii of different natural proteins.

Matrix proteins, as e.g. porine or spectrin have isolated and appear to play an important role in the function of membrane pores and their transport characteristics ***(Benz et al.,; Grander and Bennett, 1989).***

Membrane components:

Membrane components are lipids, proteins and carbohydrates.

[A] Lipids:

Three major classes of lipids are present in animal cell membranes, they are, phospholipids, cholesterol and glycolipids. In keeping with the fluid mosaic model, this lipid molecules are arranged with their polar head groups towards the aquous interface and their fatty acid chains meeting in the centre, so that the long axis of the lipid molecule is perpendicular to the plane of the membrane (Fig. 1).

A typical phospholipid molecule has two hydrophobic hydrocarbon tails, which vary in length and normally consist of 14-24 carbon atoms. One chain is usually unsaturated and has one or more cis-double bonds resulting in a "bend" in one tail, while the other is saturated. These differences in tail length and

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saturation, influence the fluidity of the membrane ***(Quinn and Chapman, 1980)***

The two hydrocarbon chains are esterified via a glycerol molecule and phosphate ester, to a hydrophilic base. In glycerolipids, the glycerol is esterified directly to the carbohydrate units. Cholesterol molecules are oriented with their hydroxyl groups close to the polar head groups of the phospholipids molecules, and their steroid rings interact with, and partly immobilize those regions of the hydrocarbon tails closest to the head groups ***(Albert et al., 1983)***.

The cholesterol contents of the membrane also influence its fluidity. At 37°C, cholesterol tends to make the membrane less fluid. However, at low membranes temperatures, cholesterol conserves fluidity ***(Darnell et al., 1986)***.

[B] Proteins:

Specific membrane processed are carried out largely by membrane proteins. The amount and type of proteins reflect the functions of the membrane. For example, the protein content of myelin sheath is approximately 18% of the dry weight of the membrane, whereas the internal membranes of mitochondria are approximately 76% protein. Most plasma membranes are approximately 50% proteins (Table (1)

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Membrane	Proteins	Lipid	Carbohydrate
* Myelin	18	49	3
* Plasma membrane			
Human erythrocytes	49	43	8
Human platelets	33-42	58-51	7.5
Mouse liver cells	44	52	4
* Mitochondrial Inner membrane	76	24	0
* Sarcoplasmic reticulum	67	33	0

Membrane proteins can be classified as "peripheral" or "integral" depending upon the case with which they can be removed from the membrane (Fig. 1). Peripheral membrane proteins, such as cytochrome C of mitochondrial membranes, can be washed off the membrane using buffers, whereas integral proteins require detergents or organic solvents for extraction. Aproximately 70% of membrane proteins are integral proteins. Those that span the membrane and are exposed to an aqueous environment on both sides are termed as "transmembrane proteins". These may be fibrous or globular. Because water is excluded from the interior of the membrane, polar groups of polypeptide chains form hydrogen bonds with each other, and these chains are therefore arranged mainly as α-helices or ß-sheets. Fibrous proteins usually have only a single α-helical strand of polypeptide spanning the hydrophobic segment of membrane and are often heavily glycosylated on the extracytoplasmic surface. Globular proteins have many loops of polypeptide chain spanning the membrane and a much higher percentage of hydrophobic surface. Most tend to have a dimetric structure ***(Klingenberg, 1981)*** and are probably transport proteins. The protein, band 3 of the

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