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A REVIEW: MOLECULAR MECHANISM: TO STUDY DRUG LIPID INTERACTION

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ABSTRACT

Since Singer and Nicolson's fluid mosaic model was introduced, our understanding of membrane organization has evolved. Rather than being homogeneous bilayers of lipids dispersed uniformly, plasma membranes are actually lipid complexes with laterally separated membrane domains, such as caveolae and lipid rafts. The pharmacokinetic features of medications, including their transport, distribution, and accumulation, ultimately impact their efficacy. Research conducted in both in vivo and cell culture settings has demonstrated the critical role that drug-lipid interactions play in these processes. Drug effectiveness can be estimated using liposome model membrane systems in a variety of ways. Estimating the quantity of drug carried into cells as well as its route of transport is also possible with lipid model membranes.

The aim of the experiment is to study molecular mechanism of drug lipid interaction

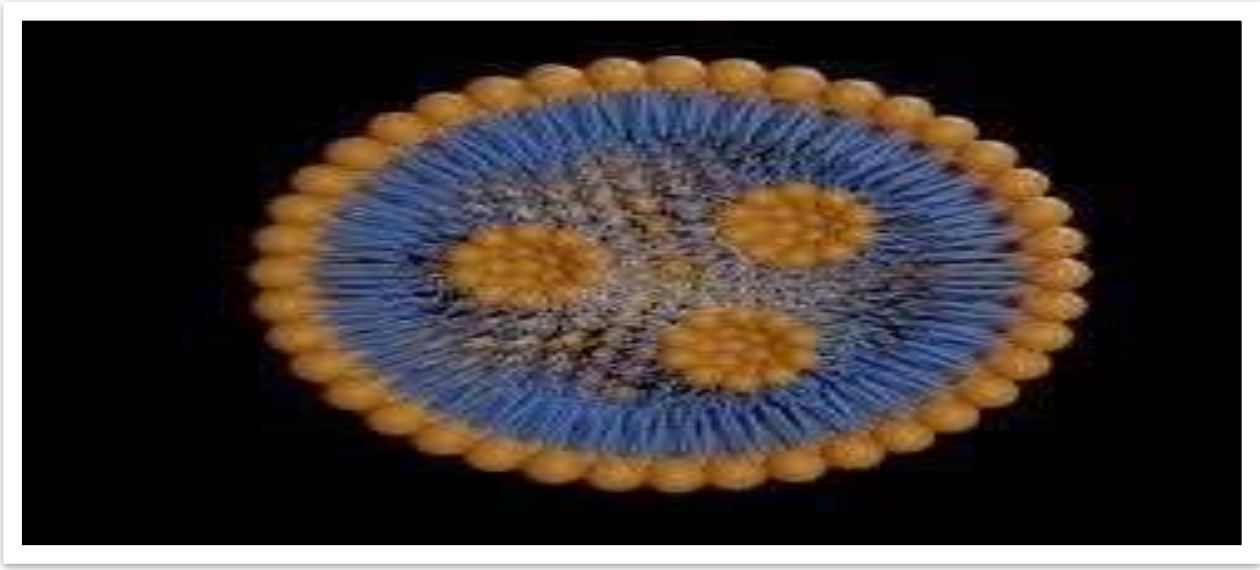


Fig 1 : Liposome

REVIEW OF LITERATURE

1. **AM Seddon, D Casey(1)** The field of drug–membrane interactions is one that spans a wide range of scientific disciplines, from synthetic chemistry, through biophysics to pharmacology. Cell membranes are complex dynamic systems whose structures can be affected by drug molecules and in turn can affect the pharmacological properties of the drugs being administered. In this tutorial review we aim to provide a guide for those new to the area of drug–membrane interactions and present an introduction to areas of this topic which need to be considered …
2. **Jumper, R Evans, A Pritzel, T Green, M Figurnov(2**) Proteins are essential to life, and understanding their structure can facilitate a mechanistic understanding of their function. Through an enormous experimental effort 1, 2, 3, 4, the structures of around 100,000 unique proteins have been determined 5, but this represents a small fraction of the billions of known protein sequences 6, 7.

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Structural coverage is bottlenecked by the months to years of painstaking effort required to determine a single protein structure. Accurate computational approaches are needed to address this gap.

3. **A Kusumi, TK Fujiwara, R Chadda(3)** The recent rapid accumulation of knowledge on the dynamics and structure of the plasma membrane has prompted major modifications of the textbook fluid-mosaic model. However, because the new data have been obtained in a variety of research contexts using various biological paradigms, the impact of the critical conceptual modifications on biomedical research and development has been limited**.**
4. **LJ Pike - Journal of lipid research, 2006 – ASBMB(4)** The recent Keystone Symposium on Lipid Rafts and Cell Function (March 23–28, 2006 in Steamboat Springs, CO) brought together biophysicists, biochemists, and cell biologists to discuss the structure and function of lipid rafts. What emerged from the meeting was a consensus definition of a membrane raft:" Membrane rafts are small (10– 200 nm), heterogeneous, highly dynamic, sterol-and sphingolipid-enriched domains that compartmentalize cellular processes. Small rafts can sometimes be stabilized.
5. **TPW McMullen, RNAH Lewis(5)** The existence of relatively large and longlived detergent-insoluble, sphingolipid-and cholesterol-enriched, liquid-ordered lipid raft domains in the plasma membranes of eukaryotic cells has become widely accepted. However, we believe that the evidence for their existence is not compelling despite extensive work on both lipid bilayer model and biological membranes. We review here the results of recent studies, which in our view call into question the existence of lipid rafts in membranes, at least in the form commonly

INTRODUCTION

The primary components of the cell membrane, which are a wide range of distinct lipids, proteins, and polysaccharides, make it an extremely complex and diversified system. Amphipathic phospholipids make up the majority of the continuous lipid bilayer matrix found in cell membranes. The cell membrane, which acts as a cell's border, is crucial to a drug's absorption, distribution, metabolism, and excretion (ADME).[1] With the solution to the sequence problem, the general structure for a single protein domain has been found, marking the most spectacular enormous leap forward in life science since the identification of the double helix structure of DNA.[2] The idea of membrane organization has evolved gradually since Singer and Nicolson proposed a fluid mosaic model; in this model, lipid complexes with laterally separated membrane domains, such as lipid rafts and caveolae, constitute plasma membranes rather than homogeneous bilayers of uniformly distributed lipids.[3] Lipid rafts are membrane domains that are different from other membrane structures, being tiny (10-200 nm), diverse, dynamic, and high in sphingolipids and cholesterol.[4] Because they divide membranes into functional sections and give membrane proteins a place to reside, lipid raft membrane domains are crucial for cellular signal transduction and trafficking.[5-8] Membrane lipid rafts and caveolae are localized or host clusters of pharmacologically significant receptors, ion channels, and enzymes.[9-12] The route of pharmacological action can first be understood in terms of the straightforward receptor/channel/enzyme and ligand interaction described in the classic mechanistic theory, given the placement of receptors, ion channels, and enzymes in membrane lipid rafts. The second idea is that medications could alter the organizational integrity of lipid rafts by acting on membrane lipids, which would modify the activity of ion channels, enzymes, and receptors that are embedded in membrane domains. If medications interact more favorably with lipid rafts than with non-raft overall membrane lipid bilayers, it would be interesting to find out if this interaction at the membrane lipid level is connected to the pharmacological and cytotoxic effects of drugs. Although cholesterol is necessary for the creation of rafts and caveolas, the regulating effects of membrane domains on ion channels and receptors were verified by lowering the amount of cholesterol in plasma membranes.13-16

General mechanisms of Drug-Membrane Interactions

Passive Diffusion

According to Fick's law, passive diffusion is the net transfer of chemicals from a high concentration area to a low concentration area. It is a major route for the penetration and absorption of drugs. Drug molecules can contact their binding sites contained in the lipid bilayer by either directly crossing the membrane or diffusing laterally through the membrane.[17-18] A drug's concentration gradient or its difference in saturation degree, or equilibrium solubility, between the two sides of the membrane can be the driving force behind passive diffusion. [19] Because of their capacity to interact with the hydrophobic tail of the lipid bilayer, small hydrophobic drug molecules can diffuse across the plasma membrane quickly. In contrast, unless they are very small and have an ideal net charge, hydrophilic or ionized molecules do not readily diffuse across the bilayer.[20-21] Conversely, high hydrophobicity hinders the bioavailability of the active medicinal components since it may cause them to be stuck in the lipid membrane due to strong hydrophobic bonding. The integrity of the membrane as a protective barrier is discovered to be destroyed by this unwanted drug-membrane binding. [22] Consequently, the medicine must have the best possible affinity—or lipophilicity—for the lipophilic membrane environment.

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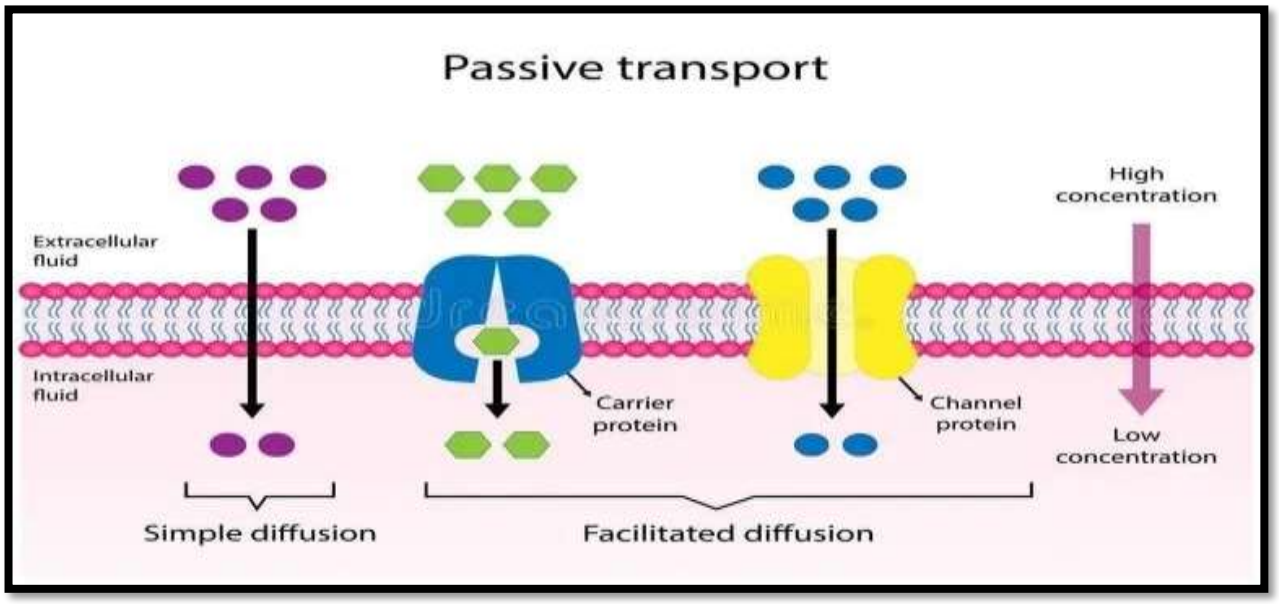


Fig 2 : Passive diffusion

Protein- Mediated Transport

This form of transport is facilitated by certain membrane proteins that offer continuous protein-lined routes through lipid bilayers, allowing some drug molecules to enter or exit cells more easily. The two primary protein types implicated in this kind of transport are typically classified as carriers or channels. In facilitated diffusion, channel proteins create pores in the membrane that permit water-soluble molecules—those that are charged or have polar groups—to flow through, whereas carrier proteins literally alter their structure to facilitate the passage of particular molecules across membranes in a process known as active transport. **Interactions Of Model Lipid Membrane With Drug :**

It is unavoidable for drug-lipid interactions to occur since many drug molecules have intracellular targets, which means they must cross one or more phospholipid bilayers in order to reach the intracellular targets and cause a reaction. Research in both in vivo and cell culture settings has demonstrated the importance of drug-lipid interactions in the pharmacokinetic (transport, distribution, and accumulation) aspects of drug action, which in turn affect the medications' overall effectiveness. Therefore, in order to produce powerful medications, it is essential to comprehend how these interactions affect the pharmacokinetic features of drugs. **Drug :**

Antibiotics :

Better explanations for the findings from in vivo and cell culture experiments have been offered by biophysical research. In J774 macrophage cells, for example, Michot et al.[23] found appreciable variations in the cellular accumulation and intracellular activity of four closely similar fluoroquinolone derivatives, in the following order: ciprofloxacin < levofloxacin < garenoxacin < moxifloxacin. Ciprofloxacin efflux in J774 macrophages was found to be the cause of the lower ciprofloxacin accumulation as compared to moxifloxacin acquisition.[24] It was unknown, meanwhile, why the ciprofloxacin transporter showed varying susceptibilities to efflux. The contrasts between the two medications' cellular accumulation and intracellular activity were explained by biophysical studies of the interactions of fluoroquinolone derivatives (moxifloxacin and ciprofloxacin) with lipid model membranes.[25-27]

Antifungal Drugs

Using Langmuir model membranes, Corvis et al.[28] investigated the behavior of griseofulvin, an antifungal drug, at a biologically analogous SP of 30 mN/m. It was proposed that the cell membrane's capacity to identify a specific molecule may play a role in the mechanism of action of griseofulvin.

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Antipsychotic Drugs

Hidalgo et al.[29] examined how the antipsychotic medications trifluoperazine and chlorpromazine affected lipid monolayers, discovering that even minute amounts of these medications cause surface potential and SP to alter. The authors deduced from this data that the lipids have to respond to these medications cooperatively; yet, the binding of these pharmaceuticals results in modifications to several lipids that go well beyond the site of drug binding. The method by which these medications exert relatively nonspecific effects over the lipid membrane may be explained by the cooperative action of the lipid membrane, as revealed in our work.

Liposome Model Membranes As Prediators Of Drug Efficacy

Drug efficacy evaluations frequently employ liposome model membrane systems. The partition coefficient, a measurement of the quantity of a drug that will permeate and/or pass across a lipid membrane into a biological system, is typically used to assess the efficacy of pharmaceuticals. When estimating partition coefficients for pharmaceuticals, an isotropic two-phase solvent solution, like a combination of octanol and water, is typically used. [30] According to a number of studies, liposome model membranes are a more accurate substitute for conventional partition coefficient estimation techniques because the latter are unable to take into consideration potential ionic interactions between medications and lipids, especially when the pharmaceuticals are charged. In the case of Rodrigues et al.[31] rifampicin and dibucaine, which are ionized at physiological pH, were found to have different partition coefficient values with water-dimyristoyl-L-α-phosphatidylglycerol (DMPG) (anionic liposome) and water-DMPC (zwitterionic liposome) compared to neutral drugs, which displayed similar partition coefficient values in both water-DMPG and water-DMPC systems. Electrostatic interactions between the head groups of lipids and ionized drugs—that is, the interaction between cationic dibucaine and anionic DMPG head groups— were the reason for the variation in partition coefficient values. The findings indicate that liposomes, as opposed to octanol-water, provide superior systems for measuring partition coefficients due to their ability to replicate the hydrophobic portion and the externally charged polar surface of phospholipids found in natural membranes.

Estimating the quantity of drug carried into cells as well as its route of transport is also possible with lipid model membranes. Using a variety of biophysical methods, Baciu et al. [32] investigated the interactions between cationic amphiphilic drugs (CADs) and lipid model membranes. The findings demonstrated that active transport and diffusion are not the only mechanisms underlying CADs. It was demonstrated that CADs caused the double-chain PCs to split into mono-chain PCs and fatty acid via this process. When monochain PCs are concentrated enough, they can form micelles that can move the medication to other intracellular membranes by separating from the membrane.

Additionally, model membranes have been employed to study the toxicity process, especially at drug concentrations that have been shown to be harmful in vivo. Amphotericin B (AmB) is an antibiotic with potent antifungal properties that is very hazardous to mammalian cells. [33,34]

Interactions Of Plymers And Drug Delivery Systems With Lipid Membrane

It has been demonstrated that the interfacial characteristics of polymeric coatings applied to drug delivery systems or the drug delivery systems themselves affect how well the systems interact with biological environments and, in turn, how well they deliver biotherapeutic agents to cells and tissue. Several polymers, such as poly(vinyl alcohol) (PVA)[35],poly(ethylene oxide) (PEO)[36],chitosan[37], are utilized as coatings in the creation of drug delivery devices. It has been demonstrated that the size of drug delivery systems and physical properties of these polymers, such as their hydrophilicity, hydrophobicity, and surface charge, can greatly affect how efficiently they interact with lipids. The effectiveness of drug delivery systems in delivering biotherapeutic drugs to cells and tissue can be affected by these polymers in one of two ways. To effectively construct drug carrier systems and gain a deeper comprehension of the mechanisms underlying drug delivery system absorption or harmful effects, a more comprehensive understanding of the interactions between lipid-drug delivery systems and polymers is therefore important. The degree of disruption caused by PAMAM dendrimers in lipid bilayers is dependent on their size and charge, as demonstrated by a biophysical analysis of the interactions between SLBs and amine-terminated generation 7 and 5 (G7 and G5) poly(amidoamine) dendrimers. [38-40]

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CONCLUSION

The transport of pharmaceuticals and drug delivery systems across biological barriers can be better understood by means of straightforward yet efficient drug lipid interaction investigations conducted with model membranes. Druglipid interaction studies using model membranes may offer a sensible method for both drug development and discovery, as well as for creating effective drug delivery systems, with a deeper comprehension of the mechanisms of interactions.

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