Drug–Membrane Interactions. Analysis, Drug Distribution, Modelling, Methods and Principles in Medicinal Chemistry. By *Joachim K. Seydel* and *Michael Wiese.* (Series: "Methods and Principles in Medicinal Chemistry", Vol. 15 by R. Mannhold, H. Kubinyi and G. Folkers.) Wiley-VCH, Weinheim 2002. 349 pp., hardcover € 139.00.—ISBN 3-527-30427-4

The editors explain that "the book is written for medicinal chemists who show interest in drug-membrane interactions". Although I am not a medicinal chemist, I previously had an opinion about the activity of drugs. I thought that they only interacted with proteins or nucleic acids, membranes being only involved as transport or barrier systems. However, this book provides surprising insights into the detailed structure of widely different types of biological membranes, the protein–lipid–steroid interactions which occur, and how some important drugs interfere. Thus everybody who is interested at all in lipid membranes will learn a great deal from it.

The table of contents lists sections on the organization of lipid membranes (30 pp.,), octanol–water partitioning and pharmacokinetics (85 pp.), specific drug–membrane interactions (70 pp.), and computer simulations (40 pp.). The main interest which the book evokes and satisfies lies in the relatively detailed discussions of particular membrane components and their interactions with drugs. The following eight examples from different parts of the book should serve to illustrate them and point out interesting aspects to the potential reader.

1. A mixture of anionic and cationic peptides induces rapid and efficient fusion of egg lecithin vesicles. No fusion occurs with either peptide alone, because only the mixture has an ordered helical structure within the membrane.

2. Fungal membranes contain ergosterol instead of cholesterol. Inhibition of ergosterol synthesis is therefore a successful method of antifungal therapy.

3. ^{45}Ca ions bind to negatively charged phosphatidylserine monolayers. Hydrophobic local anesthetics, usually amphiphilic amines, replace them efficiently, and $^{45}Ca^{2+}$ radioactivity migrates into the bulk water.

4. NMR experiments show that anesthetic steroids are much more mobile than derivatives of low biological activity. The small anesthetic molecule Halothane fluidizes membranes and thereby favors the closing of sodium channels. The "high-volume" fluid phase is unable to expand. Another local anesthetic, methoxyfluorane, forms domains only on the membrane's surface.

5. The biosynthesis of low-density-lipoprotein cholesterol is best blocked by inhibiting the enzyme HMG-CoA reductase in liver tissue only. This can be achieved by choosing relatively hydrophilic inhibitors with octanol–water coefficients (= CLOGP) less than 2. This corresponds to the character of liver membranes.

6. 5-Benzylpyrimidines are effective in killing gram-negative bacteria only if their substituents reach down from the surface phosphate groups, where the pyrimidines form salts, to the lipid A.

7. Chlorpromazine, a 1,3-diaminopropane with an anthracene-like substituted nitrogen atom, integrates into the DPPC vesicle's head group region and thereby induces an interdigitated bilayer of 30 Å thickness instead of the usual 50 Å bilayer.

8. Mefloquine accumulates in membranes, because its trifluoromethyl substituents are readily soluble there. This fact may explain its ability to kill chloroquine-resistant strains of *Plasmodia* in malaria treatment.

Thus, the book makes it clear that many important drugs do not simply migrate through membranes to hit target proteins and destroy their activity. Instead they often remain localized on the surface of intrinsic membrane proteins or the membranes themselves and can then also radically alter the properties of the fluid bilayers of mammalian cells or the permeability of more complicated arrangements in bacterial membranes. Model calculations have so far mostly been concerned with pore formation by peptides and with short-term molecular dynamics, aspects which seem to be of limited interest with respect to drug activity.

Thus, many phenomena of pharmacology, from anesthesia to the lowering of cholesterol levels, from the selectivity of antibiotics to cell fusion, can be traced back to the interplay between lipids, proteins, and drugs, often giving important new insights, and therefore this book is of extraordinary interest.

There are, of course, some minor difficulties in reading the book. The list of abbreviations is incomplete. It does not include CHOL, CHAPS, HMG, or CLOG-P, which occur frequently in the text. Structural formulas are difficult to find. For example, amiodarone (**1**), nimodipine (**2**), and propanolol (**3**) are discussed and compared on page 203, but the structural formula of **1** appears on page 109, that of **2** is not given at all, and that of **3** is hidden in an illustration on page 42. From a scientific viewpoint I regretted that there was no discussion of the peculiarity of the cholesterol structure in contrast to that of phytosterols or ergosterol. This seems quite important in the context of the book. Observed stereoselectivities (mostly between diastereomers) are occasionally mentioned, but not explained.

On the whole, however, the book is well written and succeeds in achieving its aims. The title of the book does not lead one to expect anything more than pharmacokinetics, but in fact one finds a wealth of surprising and important information on molecular interactions and the means to detect them. As far as I know, the book has no real competitor. Related reviews and monographs deal with pharmacokinetics and fluidity changes of membranes as determined by NMR spectroscopy, but do not really relate to the action of the drugs. I recommend buying the book.

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