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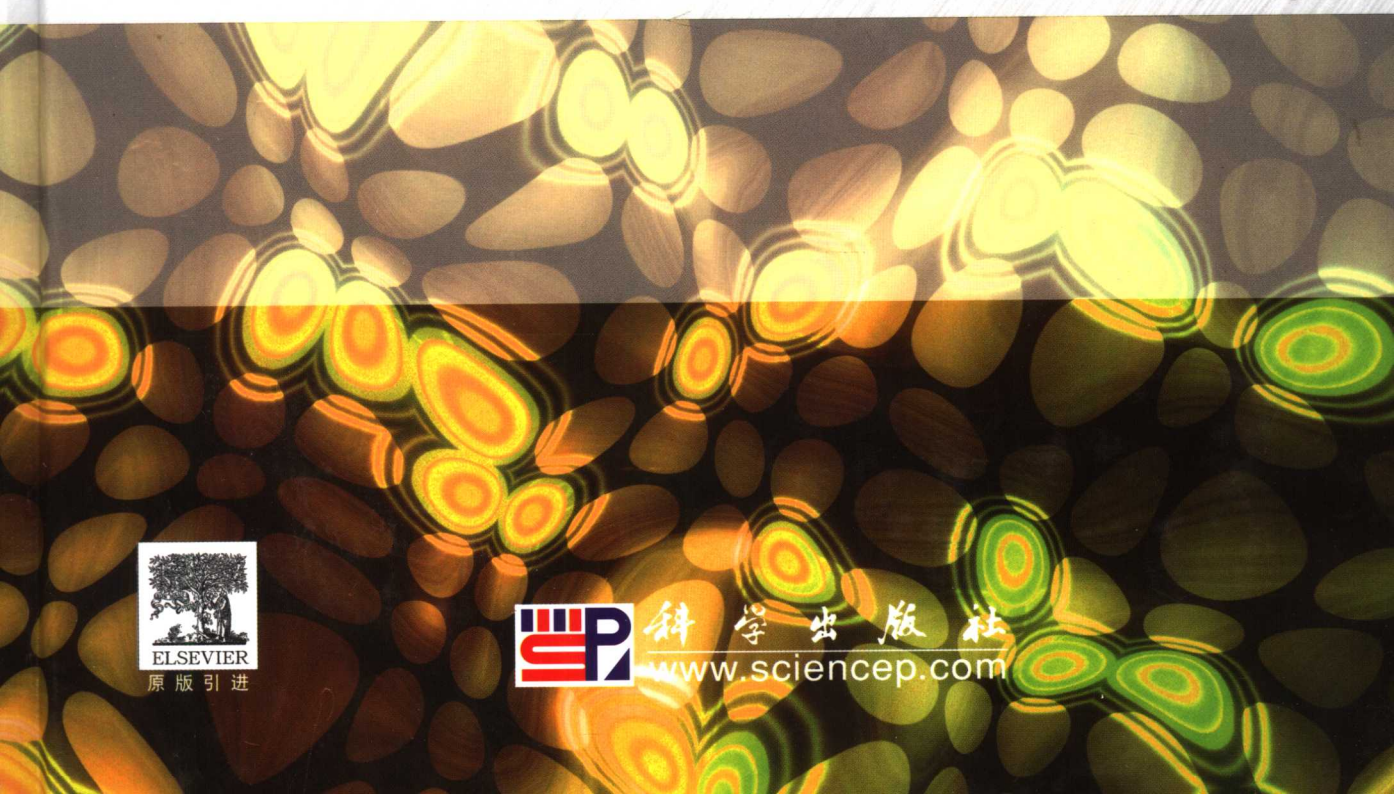
Surface Activity in Drug Action

表面活性与药物作用机制

R.C. Srivastava and A.N. Nagappa



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导 读

表面活性现象广泛存在于生命体系中，对于表面现象的研究具有重要的理论和应用价值。以前的表面科学研究很少涉及到生命科学领域，特别是药物研究领域。随着分子生物学思想的萌发和壮大，人们开始利用表面科学来研究生物学现象。具有表面活性的分子对于生命体及其组织具有至关重要的作用。本书第一次以专著的形式介绍了药物作用的液膜假说，其核心思想是：许多药物具有表面活性，它可以在界面聚集并在作用位点形成薄膜充当渗透屏障，阻止某些有关物质分子向受体部位渗透，从而发挥药效。由于有关液膜假说的研究仅见于文献报道，并在一系列药物上得到了验证，但也还有待进一步更为广泛的研究与论证。因此，本书的参考意义是很大的，其启发价值也是毋庸置疑的。

全书围绕着液膜假说进行了详细而系统的阐述，具有科学性、系统性和前沿性。本书的内容主要包括三个方面：(1) 背景介绍：第 1 章简要介绍液膜假说和研究范围，第 2 章和第 3 章分别介绍了具有表面活性的各类药物和现有的药物作用机制理论；(2) 液膜假说的内容：作者在第 4 章中提出了药物作用的液膜假说，并在后续两章中分两个方面进行了详细的论述。第 5 章介绍了脂质双层膜模拟生物膜的研究，第 6 章中则以事实说话，列举了大量有关液膜假说的实验，并从实验的设计思路开始进行了详细的介绍。列举的研究对象涉及了大量具有不同药理作用的模型药物。借此，读者可以循着研究人员的足迹，一步一步的了解液膜假说的发生和发展。液膜假说是从一个全新的角度来审视药物的作用机制，并与现有的占领学说理论和速率理论有着相通之处，在第 7 章中，著者将液膜假说和现有的药物作用机制学说进行了对比；(3) 液膜假说的应用：对于药学研究人员来说，第 8 章是很值得一读的。作者对表面活性剂在药学研究领域的应用作了一个较为全面的综述，主要包括药物吸收和药物递送两部分，内容涵盖了当今研究的热点，如吸收促进剂、基因递送体系、脂质体和纳米粒等。

科学出版社本次引进的这本专著独辟蹊径，以药物表面活性的思想来研究药物的作用机制，对现有的药理学、药物作用机理的研究是一个很好的新思路。另外，本书很好的体现了学科交叉的特性，内容涉及了生物化学、物理化学、药理学和药剂学的基本知识，并在其中做到了融会贯通。阅读本书，读者不仅可以获得相关的科学知识，还能从中体会到科学研究的思路，领悟到现代科学实验的方法。本书可以作为医药学高校教师、科研院所、医药企业的专业研究人员学习和工作的参考书，也适合医药学研究生和高年级本科生在进行论文研究时参考，当然，作为医药院校研究生的学位课程用书也是可行的。

吕万良

2006 年 11 月于北京大学药学院

前　言

表面活性广泛存在于生命系统中。以体液或细胞液为例，其表面张力往往小于水的表面张力。大多数双分子，蛋白质，脂质等都具有表面活性。具有表面活性的分子对于生命体及其组织具有至关重要的作用。细胞的形成实际上就是表面活性作用的结果。生命系统中的表面现象是进化的产物，也就是说，表面活性依据需要而产生，因而其应当在生物反应中起到重要的作用。

正是基于以上思考，我们将该领域的研究着手整理并编辑成书。

既然细胞膜的形成和受体蛋白在脂质双分子层中的定位是表面活性作用的结果，药物与细胞膜相互作用后改变了细胞膜的通透性，然后发挥药效作用，我们有理由推测药物发挥效应可能也是表面活性作用的结果。事实上就是如此，有足够证据表明，所有表面活性药物发挥药效的作用机制中，通常某些关键性步骤可能是相同的。表面活性药物很可能聚集在界面并在作用位点形成液膜，阻碍相关分子接近靶点，从而发挥药理作用。我们对大量具有不同药理作用的药物进行研究发现，药物在靶点处形成的液膜可阻碍相关分子接近，对于药物发挥作用有很重要的意义，液膜的阻碍作用是表面活性药物的作用机制中的一个重要步骤。在研究的基础上，我们提出了针对表面活性药物的“药物作用的液膜假说”。在本书的第 1 章至第 7 章中阐述了该假说的内容。第 8 章介绍了表面活性作用在治疗学方面的应用。

本书涉及的工作得到了几个国家基金机构的资助，这些机构包括科学与工业研究理事会（CSIR）、科学技术部（DST）、印度政府以及全印技术教育理事会与大学基金委员会。在此对以上基金委员会的支持表示感谢。

笔者的一部分同事和有关研究人员也参与了本专著的编写工作。主要有 S. B. Bhise 博士，C. V. S. Subrahmanyam 博士，D. B. Raju 博士，A. K. Das 博士和 A. N. Nagappa 博士。特别感谢本书的参编作者 S. B. Bhise 博士，他在其博士学位论文研究期间，首先将该领域的问题进行了研究。作为主编，笔者（RCS）还要特别感谢共同主编 A. N. Nagappa 博士，是他建议撰写一本介绍药物作用的液膜假说相关理论的专著。

本书完成于印度博拉理工学院（BITS，印度拉贾斯坦邦），此时第一作者在该学院担任长期教职（tenure），并兼任印度博拉理工学院大学基金委员会的荣誉会员。在此，笔者对新德里大学基金委员会的资助和作为承担单位的印度博拉理工学院的热情接待表示衷心的感谢。特别感谢印度博拉理工学院副校长 S. Venkateswaran 博士、L. K. Maheshwari 博士和其他领导的关心。

Ramesh Sharma 小姐承担了文字处理和图片扫描工作，K. N. Sharma 小姐承担了本书的绘图工作，在此对她们的辛勤劳动表示感谢。

我们的精神动力还来自于两位可爱的小天使：Krishnapriya（KP）和 Vaishnavi（V），她们使我们永葆激情，我们将这本书献给她们。Krishnapriya 是笔者（主编

RCS）的孙女，Vaishnavi是共同主编ANN的女儿。根据印度的传统，学生就像老师的儿子一样，因此，笔者将ANN的女儿Vaishnavi也视为自己的孙女一般。

（北京大学药学院　刘扬　译　吕万良　校）

To
K.P. and V.

PREFACE

Surface activity is of ubiquitous presence in living systems. Take any body fluid or cell soup, its surface tension is always less than that of water. Most of the bimolecules, proteins, lipids etc. are surface active in nature. Molecules of surface-active nature are crucial to living matter and its organization. Formation of biological cell is as a matter of fact, a consequence of surface activity. Surface activity in living systems is a matter of evolution i.e., it is need based and therefore should have a crucial role to play in biological actions.

With this thought in mind the investigations recorded in this monograph were started.

Since formation of cell membranes and location of receptor proteins in the lipid bilayer are a consequence of surface activity, it is logical to expect that the drugs acting by altering the permeability of cell membranes after interacting with them may also be surface active in nature. In fact they are, and there is enough circumstantial evidence to indicate that there may exist some crucial step common to the mechanism of action of all surface-active drugs. Surface-active drugs are likely to accumulate at the interface and form films at the site of action modifying access of relevant molecules to the action sites. Our investigations on a wide variety of drugs belonging to different pharmacological categories have revealed that the modification in the access of relevant molecules to the site of action is an important step common to the mechanism of the surface-active drugs and makes significant contribution to drug action. In fact these studies have led us to propose "a liquid membrane hypothesis of drug action" for surface-active drugs. Chapters 1 to 7 contains an account of the hypothesis. Chapter 8 contains a general account of the application of surface activity in therapeutics; this chapter has been added for the sake of completeness of the monograph.

The work recorded in this monograph has been funded by several National Funding Agencies namely the Council of Scientific and Industrial Research (CSIR), the Department of Science and Technology (DST), Government of India, All India Council for Technical Education and the University Grants Commission. The support received from different funding agencies is gratefully acknowledged.

A number of colleagues and associates have participated in the research recorded in this monograph. Some of the prominent names are Drs. S.B. Bhise, C.V.S. Subrahmanyam, D.B. Raju, A.K. Das and A.N. Nagappa; the present co-author. Especial thanks are due to Dr. S.B. Bhise who was the first to work on this problem with conviction, for his doctoral degree. I (RCS) as senior author would also like to offer especial thanks to Dr. A.N. Nagappa who suggested that a monograph be written on our work on liquid membranes in drug action.

This monograph has been written during the tenure of the first author (RCS) as an Emeritus Fellow of the University Grants Commission at the Birla Institute of Technology and Science (BITS) Pilani Rajasthan India. The support from the University Grants Commission, New Delhi and the kind hospitality of the BITS as host organization are gratefully acknowledged, particularly to the Vice-Chancellor Dr. S. Venkateswaran and Dr. L.K. Maheshwari, Director BITS for their affectionate treatment.

Thanks are due to Mr. Ramesh Sharma for word processing and scanning the figures of the manuscript and Mr. K.N. Sharma for artwork.

The inspirational force from two little angels, Krishnapriya(KP) and Vaishnavi(V) kept our zeal undamped. We dedicate this work to them: Krishnapriya is the grand daughter of RCS and Vaishnavi is daughter of ANN. According to Indian traditions, student is like a son to his teacher hence ANN's daughter, Vaishnavi, is also like a grand daughter to RCS.

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Chapter 1

Introduction and scope

1. INTRODUCTION

Formation of cell membranes and location of receptor proteins in lipid bilayers is a consequence of surface activity. It is, therefore, logical to expect that the drugs acting by altering the permeability cell membranes after interacting with them are likely to the surface active in nature. This is because the lipid bilayers with receptors in them represent the interface and the drugs interacting with them will not reach the interface unless they are surface active in nature.

A wide variety of drugs are, in fact, known to be surface active in nature [1-7]. This activity does not appear to be a fortuitous coincidence. In a number of cases excellent correlations between surface activity and biological effects have been demonstrated [8-17]. A typical correlation between surface activity and clinical activity in the case of antipsychotics is shown in Fig 1.

While investigating the actions of drugs like reserpine, prenylamine, chlorpromazine, propranalol etc., which inhibit catecholamine transport, it has been concluded [18] "irrespective of chemical structure the surface activity of psychotropic drugs mainly determines their potency to affect all kinds of membranes especially that of catecholamines storing particles".

Since structural requirements of surface activity are often similar to those for interaction of drugs with receptor sites [19], the correlations between surface activity and biological effects appear to indicate that there might exist a common mode of action for all surface active drugs or there may be at least one crucial step common to the mechanism of all surface active drugs. What can this common mode/crucial steps be?

In view of the liquid membrane hypothesis, which we will describe briefly in the next paragraph, it was suspected that the liquid membranes generated at the site of action of the respective drugs, acting as a barrier to the transcript of relevant permeants, might be an important step common to the mechanism of all surface-active drugs.

The liquid membrane hypothesis [20, 21, 22] was originally propounded to account for enhanced salt rejection in reverse osmosis due to addition of very small amounts, of the order of few ppm, of surfactants like polyvinyl methyl ether to saline feed. According to the hypothesis when a surfactant a added to an aqueous phase, the surfactant layer which forms spontaneously at the interface acts as a liquid membrane and modifies transport across the phase boundary. The hypothesis further postulated that as the concentration of the surfactant is increased the interface gets progressively covered with the surfactant layer liquid membrane and at the critical micelle concentration (CMC) of the surfactant coverage of the interface with the liquid membrane is complete. Experimental evidence from our laboratory [23-25] furnished additional support in favor of progressive coverage of the interface with the liquid membrane.