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药物发现中的药理学：了解药物反应

（导读版）

〔美〕T.P. 肯内金 著

赵 颖 导读

Pharmacology in Drug Discovery: Understanding Drug Response

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内 容 简 介

本书针对对象主要是药理学及生物技术专业在读的或毕业不久的学生，以及相关行业的低年资研究人员，他们经常需要了解化学物质何以引起生理变化。

本书用简单的方法，解释了生命体系如何利用基本的生化机制来实现对生理系统的精确化学调控。应用这些方法可以更好地预测药物在各体系中的作用，也形成了药物发现过程的基本准则。各章节合理地由浅入深，叙述了如何研究某一给定分子的药理学特性，同时给出了重要名词解释、章节内容摘要、参考文献以及复习题，帮助读者理解和复习所学内容。

This is an annotated version of
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Edited by Terry P. Kenakin

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导　读

习惯了各种版本药理学教材的内容浩繁、体积庞大，初拿到这本 *Pharmacology in Drug Discovery: Understanding Drug Response* 时，我不禁心生疑惑：这本区区二百余页的小书，能承载如此厚重的题目吗？怀着几分疑惑打开本书，简明的目录首先有些出乎我的意料，不同于同类书常见的按照生理系统划分后再逐一详述，这本书的章节划分更像一份药理学研究的重点和关键词提纲。这种耳目一新的感觉促使我继续读下去，一气读完，不禁为之赞叹：正如作者 Terry P. Kenakin 所言，这本书的写作目的，并非罗列各种药物的作用靶点和方式，而是“帮助读者解释药物的剂量—效应数据，并在分子水平进行作用机理推断”。

本书作者、北卡罗来纳州大学药学院的 Terry P. Kenakin 教授是一位资深药理学家，长期从事药物活性体外实验体系设计和定量药物受体理论研究。Kenakin 教授致力于药理学基础教学，曾编写 *A Pharmacology Primer: Theory, Application and Methods*（《药理学初级读本：理论、应用与方法》）一书并多次再版。本书是他 2012 年出版的新作。

本书内容共十章。第一章作者首先给出本书主线，即探讨“生理过程的化学控制”。在化学控制过程中，涉及药物作用的靶点、量－效关系曲线、激动剂、拮抗剂等基本要素或概念，并需要从分子水平对这些药理学现象进行解释。第二章着重描述了药物对于靶点的两个重要作用参数，即亲和力和效应，以及对产生效应的激动剂机理的分类和研究方法。第三章介绍了描述激动剂浓度与组织反应的 Black-Leff 作用模型，以及如何应用此模型预测激动剂的作用。第四章介绍了药物的拮抗作用，详细讲解了药物作用位点的竞争性、非竞争性拮抗及慢解离拮抗模式。第五章讲述别构药物作用，包括正、负别构调节作用，以及对别构作用的定量。第六章介绍了一类重要的药物作用靶点——酶，分类叙述了酶促反应动力学、酶抑制动力学，并对以酶为靶点的药物进行了简要介绍。第七、八两章从吸收、代谢、分布、清除各方面介绍了药物代谢动力学，以及对药物体内药代性质的预测。第九章体内药理学介绍了影响药物体内代谢性质的因素，以及如何将体外实验获得的数据用于体内药效的预测。第十章对药物的安全性、毒性及有效应用于早期毒性预测的方法进行了阐释。每章开头处给出提纲和关键名词解释，末尾处给出本章的总结和复习题。对于前五章理论计算性较强的内容，每章辟专节以流程图的形式描述了对本章所述及问题的研究思路，令读者一目了然。其中穿插的人物及背景介绍，让枯燥的理论知识也变得饶有趣味。

总结起来，作为一本冠以“药理学”的专业书籍，本书内容有两个重要特点。一是“解释”，将不同种类药物的作用途径模式化成为模型、公式、理论，可谓“知其然，亦知其所以然”。二是“预测”，运用这些模式化出的、具有普适性的模型、公式、理论，对新化合物或先导化合物的成药性进行预测。正所谓“授人以鱼不如授人以渔”。对于初入门的药理学学生或研究者而言，这样一本“将现象上升为理论，以理论指导实践”的小书，看似简，实则精，的确是一本很受用的教材及工具书。

感谢科学出版社的独到眼光和责任编辑的辛勤工作，使得本书能够与我国药理学工作者见面。希望这本书导读版的出版，能为我国药理学专著增加一线“不一样的风景”，为我国广大药理学工作者奉上一份“原汁原味的盛宴”，为提高药理学研究和教学水平作出一份贡献。

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中国药理学会
2013 年 3 月

前　言

在科学领域中，药理学是一门比较年轻的学科，它是在 20 世纪由一门更古老的学科——生理学分支发展而来。这一名词涵盖了从药物作用的研究到新药设计的各种涵义，这些术语间的细微差别关系着药理学如何表述和教学。对于一名医学生，药理学意味着治疗药物的性质，以及学习在治疗过程中如何使用药物（即治疗学），对研究者则可能意味着药物作用机理研究。而对于一名致力于药物发现的科学家而言，药理学的意义在于应用药物化学方法去调节生理过程，以期获得较好的治疗效果。

本书的主要对象是希望了解化学物质何以引起生理变化的学生。生理系统根据自身需要，对输入的化学信号作出不同应答，因此同一个药物对不同的生理系统，可能产生不同效应。药理学的独到之处，就在于为分析药物效应的差异以及追踪形成差异的本源提供了工具，也就是解释药物作用的分子机制。这使得预测一切体系中的药物作用成为可能，并且，由于几乎一切药物都是从远离临床治疗的实验体系中开发出来的，这种预测方法可谓药物发现中的无价之宝。希望本书可以帮助读者解释药物的剂量－效应数据，并在分子水平进行作用机理推断。

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致　谢

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Foreword

In the scheme of science, pharmacology is a relatively new scientific discipline branching off, in the last century, from the older more established science of physiology. The term can have a range of meanings from the study of drug action to the design of new drugs. These nuances in terminology are associated with the way pharmacology is presented and taught. To a medical student, pharmacology may mean the properties of therapeutic drugs and the study of how they are used in therapy (i.e., therapeutics). To a researcher it may mean the study of drug mechanism of action. To a scientist working in drug discovery, it may mean the application of medicinal chemistry to modify physiology for therapeutic benefit.

This text is designed to introduce all students who may need to interpret a change in physiology induced by a chemical substance. Physiological systems customize chemical signal input to their own needs; thus the same drug can have different effects in different physiological systems. Pharmacology is unique in that it furnishes the tools to analyze these different behaviors and trace them to their root cause, i.e., the molecular mechanism of action. This enables predictions of drug behavior to be made in all systems, an invaluable tool for drug discovery since almost all drugs are developed in test systems far removed from the therapeutic one. This text should enable the reader to interpret drug dose–response data and make mechanistic inferences at the molecular level.

Terry Kenakin Ph.D.
Research Triangle Park, 2011

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I wish specifically to thank Kristine Jones and April Graham of Elsevier for patient support of this project and so very much help. I also wish to thank Dr. Angela Finch, University of Sydney, for valuable comments and guidance. The excellent artwork of Candy Webster was indispensable in the production of this book and I wish to thank her for her wonderful efforts. I am indebted to GlaxoSmithKline for support during the preparation of this book and to the University of North Carolina School of Medicine for giving me the means to explore pharmacology and apply it to drug discovery. Finally, I am very grateful to my wife and family for boundless patience during the writing of this book.

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CHAPTER

1

Pharmacology: The Chemical Control of Physiology

OUTLINE

Pharmacology and Cellular Drug Response	1	Linking Observed Pharmacology With Molecular Mechanism	12
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By the end of this chapter the reader should be able to understand how drug response is quantified by the use of dose–response curves, the way in which different tissues process drug stimulus to provide tissue response and what qualifies a drug to be classified either as an agonist or antagonist.

PHARMACOLOGY AND CELLULAR DRUG RESPONSE

Pharmacology (from the Greek φαρμακον, pharmakon, "drug" and -λογία, -logia, the study of) concerns drug action on physiological systems (physiology from the Greek φύσις, physis, "nature, origin" and -λογία, -logia is the study of the mechanical, physical and biochemical functions of living organisms). With regard to the application of pharmacology to the discovery of drugs for therapeutic benefit, the main focus of pharmacological theories, procedures and mechanisms relates to the ***chemical control of physiological processes.*** Insofar as the understanding of these physiological processes benefits the pharmacologic pursuit of drugs, pharmacology and physiology are intimately related. However, it will also be seen that complete understanding of the physiologic processes involved is ***not*** a prerequisite to the effective use of pharmacology in the drug discovery process. In fact, often an operational approach is utilized whereby the complexity of the physiology is represented by simple surrogate mathematical functions.

A unique feature of pharmacology is that the effect of the drug is often observed indirectly, that is, while the drug affects a select

biochemical process in the cell, the outcome to an observer is an overall change in the state of the whole organism, and this is often the result of multiple interacting cellular processes. A major aim of pharmacology is to define the molecular events in initiating drug effects, since these define the action of drugs in all systems. If quantified correctly, this information can be used to predict drug effect at the pharmacological target in all systems including therapeutic one(s). At this point, it is useful to define what is meant by pharmacological target.

NEW TERMINOLOGY

The following new terms will be introduced in this chapter:

- **Affinity**: The propensity of a drug molecule to associate closely with a drug target.
- **Agonists**: Drugs that produce an observable change in the state of a physiological system.
- **Antagonists**: Drugs that may not produce a direct effect, but do interfere with the production of cellular response to an agonist.
- **Dose–response curve**: The relationship between doses (if the drug is used *in vivo*) or concentrations (if used *in vitro*) of a drug and pharmacologic effect.
- **Drug target**: The protein (or in some cases DNA, mRNA) to which a drug binds to elicit whatever pharmacologic effect it will produce. These proteins can be seven transmembrane (or one transmembrane) receptors, enzymes, nuclear receptors, ion channels or transport proteins.
- **EC_{50}**: Concentration of agonist producing half the maximal response to the same agonist; usually expressed for calculation and statistical manipulation as the pEC_{50}, negative logarithm of the molar concentration producing 50% response.
- **Efficacy**: The change in state of the drug target upon binding of a drug.
- **Efficiency of target coupling**: The relationship between the net quanta of activation given to a cell and the number of drug targets available for activation.
- **Full agonists**: Agonists that produce the full maximal response that the system can produce.
- **Null method**: The comparison of equiactive concentrations (or doses) of drug to cancel the cell-based processing of drug response. The assumption is that equal responses to a given agonist are processed in an identical manner by the cell.
- **Partial agonists**: Agonists that produce a maximal response that is of lower magnitude than the maximal response that the system can produce to maximal stimulation.
- **pEC_{50}**: The negative logarithm of EC_{50} values. For arithmetic and/or statistical manipulation, numbers must be normally distributed. This is true only of pEC_{50}s, not of EC_{50}s; thus all averages, estimates or error and statistical procedures must use pEC_{50}.
- **Potency**: The concentration (usually molar) of drug needed to produce a defined response or effect.
- **Target density**: The concentration of drug targets at the site of activation, i.e., on the cell surface for receptors.

PHARMACOLOGICAL TARGETS

The term "pharmacological target" refers to the biochemical entity to which the drug first binds in the body to elicit its effect. There are a number of such entities targeted by drug molecules. In general, they can be proteins such as

receptors, enzymes, transporters, ion channels, or genetic material such as DNA. The prerequisite for pharmacologic targets is that they have the ability to discern differences in electronic structure minute enough to be present in small drug-like molecules; in this regard the most predominant targets for drugs are protein in nature. Proteins have the tertiary three-dimensional structure necessary for detailed definition of the electronic forces involved in small molecule binding. Signals are initiated through complementary binding of drug molecules to protein conformations that have a physiological purpose in the cell. The act of these molecules binding to the protein will change it, and with that change a pharmacologic effect will occur.

At this point, it is worth considering the beginning and end processes. The first process is the drug binding to the target. The result(s) of this process are totally dependent on the affinity and efficacy of the drug. These are drug parameters unique to its chemical structure. In pharmacologic terms, this is the most important effect, since it occurs in each and every tissue and organ possessing the target. Therefore, characterization of this event enables a general quantification of drug-target activity to be made in the test system, which will also be true for all systems including the therapeutic one. Therefore, ***the characterization of affinity and efficacy become the primary aim of pharmacologic analysis.*** However, it can be seen that the various (and variable) biochemical reactions linking the target to cellular response intervene, thereby causing a tissue-dependent abstraction of the link between affinity and efficacy and observed cellular potency. The magnitude of this abstraction depends upon the number of responding target units and the efficiency of target coupling.

The major protein target classes are membrane receptors, enzymes, ion channels and transporter proteins. Of these, the most prominent drug targets are receptors. While there are a number of types of receptor, one of the most important from the standpoint of therapeutic drug targets is seven transmembrane receptors (7TMRs). These are so-called because they span the cell membrane seven times to form complex recognition domains both outside and inside the cell. These proteins are capable of recognizing chemicals such as hormones and neurotransmitters present in the extracellular space, and transmit signals from these to the cell interior. Due to the fact that these are on the cell surface and thus exposed to the extracellular space, these entities were the subject of experiments that originally defined the receptor concept (see Box 1.1 for history).

Historically, while the actual physical nature of receptors was unknown, it was realized that a distinct entity on the cell surface allows cells to recognize drugs and read the chemical information encoded in them. Early concepts of receptors likened them to locks with drugs as keys (i.e., as stated by the biologist Paul Ehrlich: "*... substances can only be anchored at any particular part of the organism if they fit into the molecule of the recipient complex like a piece of mosaic finds its place in a pattern...*"). The main value of receptors is that they put order into the previously disordered world of physiology. For example, it has been observed that the hormone epinephrine produces a wealth of dissimilar physiological responses such as bronchiole muscle relaxation, cardiac muscle positive inotropy, chronotropy and lusitropy, melatonin synthesis, pancreatic, lacrimal and salivary gland secretion, decreased stomach motility, urinary bladder muscle relaxation, skeletal muscle tremor and vascular relaxation. The understanding of how such a vast array of biological responses could be mediated by a single hormone is difficult until it is realized that these processes are all mediated by the interaction of epinephrine with a single receptor protein, in this case

BOX 1.1

THE EVOLUTION OF THE RECEPTOR CONCEPT IN PHARMACOLOGY

Numerous physiologists and pharmacologists contributed to the concept of "receptor" as minimal recognition units for chemicals in cells. Paul Ehrlich (1854–1915) studied dyes and bacteria and determined that there are "chemoreceptors" (he proposed a collection of "amboreceptors," "triceptors" and "polyceptors") on parasites, cancer cells and microorganisms that could be exploited therapeutically.

John Newport Langley (1852–1926), as Chair of the Physiology Department in Cambridge, studied the drugs jaborandi (containing the alkaloid pilocarpine) and atropine. He concluded that receptors were "switches" that received and generated signals and that these switches could be activated or blocked by specific molecules.

A. J. Clark (1885–1941), who could be considered the father of modern receptor pharmacology, was one of the first to suggest from studies of acetylcholine and atropine that a unimolecular interaction occurs between a drug and a "substance on the cell." As stated by Clark: "*... it is impossible to explain the remarkable effects observed except by assuming that drugs unite with receptors of a highly specific pattern...*"

the β-adrenoceptor. Thus, when this receptor is present on the surface of any given cell it will respond to epinephrine, and the nature of that response will be determined by the encoding of the receptor excitation produced by epinephrine to the cytosolic biochemical cascades controlling cellular function. In a conceptual sense, the term "receptor" can refer to any single biological entity that responds to drugs (i.e., enzymes, ion channels, transport proteins, DNA and structures in the nucleus). This information is transmitted through changes in protein shape (conformation) i.e., the drug does not enter the cell nor does the receptor change the nature of the drug (as an enzyme would).

Pharmacologic targets can be used to modify physiological processes. Specifically, chemicals can be used to cause activation, blockade or modulation of protein receptors and ion channel targets. For enzymes and transporter proteins the main drug effect is inhibition of ongoing basal activity of these targets (Chapter 6 discusses these targets in detail). Another difference between these target classes is location; while receptors, ion channels and transporter proteins are usually found on the cell surface (exposed to the extracellular space), enzymes are most often found in the cytosol of the cell (drugs must enter the cell to act on enzymes). Exceptions to this general rule are nuclear receptors which reside in the cell nucleus. Finally, it should be recognized that there are other drug targets present in the cell, such as DNA, and that chemicals can have physical effects (i.e., membrane stabilization) that can change cellular function.

Pharmacologic effects on cells can include a wide variety of outcomes, from changes in the mechanical function of cells (i.e., cardiac contractility, contraction of bronchiole smooth muscle), biochemical metabolic effects (levels of second messengers such as calcium ion or cyclic AMP) and modulation of basal activity (level of catalytic degradation of cyclic AMP by enzymes such as phosphodiesterase, rate of uptake of neuroamines such as norepinephrine and serotonin).

It is worth considering the process of target choice in the drug discovery process. Specifically, effective prosecution of any drug target requires a minimal effort in resources and time (perhaps 1 to 2 years per target), thus it can be seen how an incorrect choice of target could lead to a serious dissimulation in the drug discovery process. While there are considerations in target choice, such as target tractability (how difficult it is to produce a molecule to alter the behavior of the target), one of the most important factors is a strong association with the disease that is being treated. It has been estimated that there are approximately 600 to 1500 possible drug targets that may be valid to pursue for therapy. These are made up of genes that are known to be associated with diseases and that also code for protein that may be modified through binding to a small molecule.[1] No discovery program could pursue a number of genes close to the number available, making target validation a very important step in the process. Table 1.1 shows some of the factors involved in the process of target validation, with particular reference to the problem of HIV-1 viral entry to cause Acquired Immune Deficiency Syndrome (AIDS). As a preface to the discussion of cellular drug effect, it is useful to consider the major pharmacological tool used to quantify it, namely, the dose–response curve.

DOSE–RESPONSE CURVES

A characteristic feature of drugs acting on a specific target in a physiological system is that there will be a graded increase in response with an increase in drug concentration (dose). If drug effect can be observed directly, then the magnitude of effect can be displayed as a function of drug concentration in the form of a dose–response curve. For example, epinephrine is known to cause increased heart rate in humans; Fig. 1.1 shows how increasing doses of epinephrine produce increases in heart rate. The curve-defining dose and resulting observed response can be used as shorthand to characterize the effect of the drug in the system. This relationship can then be used to predict what any dose of the drug will do in the system, in the form of an empirically derived line joining the observed data points. Figure 1.2 shows the increased heart rate as a function of epinephrine concentration. The lines joining the data points infer that there is a continuous relationship between epinephrine dose and heart rate. Such an empirical

TABLE 1.1 Factors Relevant to Target Validation with Reference to AIDS

Factor	CCR5 in AIDS	Reference
• Target is linked to sensitivity to disease	• CCR5 receptors must be present on cell surface for HIV-1 infection	[2,3]
• Cell level of target alters sensitivity and course of disease	• Down-regulation of CCR5 leads to resistance to HIV-1 infection	[4]
	• Genetically high levels of CCR5 lead to rapid progression to AIDS	[5]
• Interference with target will not lead to harm	• CCR5 knockout mouse[1] lacks the receptor but is otherwise healthy	[6]
• Ligands for target interfere with disease	• CCR5 interaction with chemokines interfere with HIV-1 infection	[7–11]
	• Patients with high circulating levels of chemokine have retarded progression to AIDS	[12,13]
• Specific genetic association	• Δ32 deletion in CCR5 gene leads to lack of receptor expression and complete resistance to AIDS	[14–18]

[1]*Genetically altered mouse that does not naturally express the CCR5 receptor.*

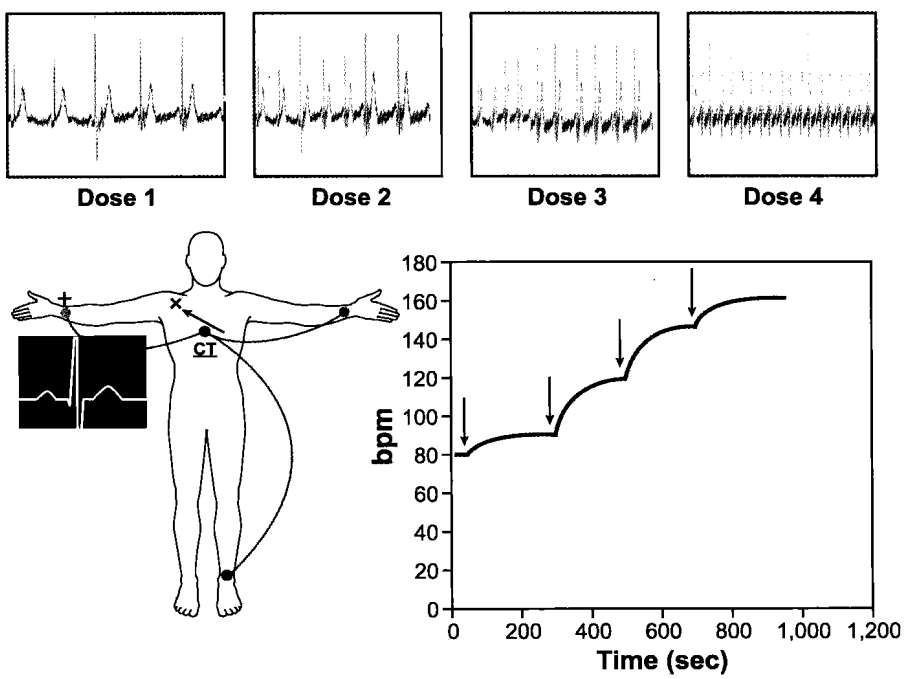

FIGURE 1.1 Dose–response curve for epinephrine given to a human at increasing doses. The heart rate is obtained from non-invasive EKG leads. It can be seen that there is a relationship between heart rate and increasing dose of epinephrine.