Roland Seifert

Basic Knowledge of Pharmacology

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Roland Seifert
Institute of Pharmacology
Hannover Medical School
Hannover
Germany

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Preface

Numerous excellent pharmacology textbooks in English language are available. These books are particularly useful for obtaining well-validated information on a specific topic. However, for a student who needs to learn the principles of pharmacology, these books have become too voluminous as the result of the explosion in knowledge. In addition, most textbooks are multi-author books, entailing different writing styles, foci, didactic concepts, and terminology.

Already, during my tenure as associate professor for Pharmacology and Toxicology at the University of Kansas, Lawrence, KS, USA (1998–2004), students had asked me to develop my lecture overheads into a concise textbook. But research kept me too busy to tackle this task. Later, at the University of Regensburg (2004–2008), I taught all aspects of basic and clinical pharmacology, and students kept on asking me to write a textbook. Again, research was a priority and prevented me from writing the book. During my tenure as professor for Pharmacology at the Hannover Medical School, teaching further professionalized with sophisticated pathophysiology- and pharmacotherapy-oriented PowerPoint slides, the plan to write "the textbook" consolidated. I made the book my priority. In August 2018, the German textbook entitled *Basiswissen Pharmakologie* appeared, and students and colleagues have adopted the book quickly.

Talking to pharmacology professors from around the world, the view corroborated that internationally there is, indeed, also the need for a concise textbook, particularly for the medical students. Based on the positive feedback from the German medical students and colleagues, I decided to develop the international textbook entitled *Basic Knowledge of Pharmacology*.

The book is primarily written for medical students, but it is certainly also useful for pharmacy students. The book is designed to complement a semester or 4–5-week block course of pharmacology (lectures in the morning, afternoon free for studying) and focuses on pharmacotherapeutic principles based on pathophysiology.

▶ Chapters 1, 2, 3, and 4 deal with the basic principles of pharmacology, drug allergy, and drug intoxications. The book covers about 400 selected drugs, discussed according to integrative systems (▶ Chaps. 5, 6, 7, 8, 9, 10, 11, and 12) and indications (▶ Chaps. 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 and 35). Clinical cases are presented as well (▶ Chap. 36). Various drug classes are discussed in different contexts (learning spiral). In the text, figures, and tables, cross-references to related content are provided. This facilitates jumping from one chapter to another. Lastly, I included a chapter (37) on 100 important drugs that every physician should know well, regardless of the specialization. With these 100 drugs, many important diseases can be treated effectively and economically.

Each chapter contains an abstract, key points, tables on the most important drugs and diseases, pathophysiology- and pharmacotherapy-oriented figures, selected key references for further reading, case studies, and MCQ exam questions. Where appropriate, tables and figures also contain key take-home messages in the legends. In the appendix, a list of drug classes and generic drugs is provided, arranged according to ▶ Chaps. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 and 35.

In the figures, green color indicates pathophysiological changes, blue color indicates pharmacotherapeutic interventions, and

red color points to toxic interventions or adverse reactions. In the book, drugs are classified according to their mechanism of action or, where more appropriate, according to their chemical properties. Traditional but imprecise, biased or outdated terms are avoided (see ▶ Chap. 1 and list of generic drugs). The book uses abbreviations (see abbreviation list) throughout. At first, the student may have to adapt to the abbreviations. But soon, the student will realize that the acronyms are helpful for precisely defining drug classes, specific drugs, drug targets, diseases, indications, adverse drug reactions, and interactions.

Pharmacology is interdisciplinary, and the knowledge in the field has expanded tremendously during the past 10 years. Very sadly, as a result of the specialization of medicine and "modernization" of curricula, in several universities, pharmacology departments have disappeared, and pharmacology has been integrated into lectures on specific organs and diseases. While this "integrative" approach is now widely adopted, the focus on pharmacology gets lost, and it just becomes an "add-on" to the clinic. However, an in-depth understanding of the mechanisms of actions of drugs is essential for understanding indications, adverse drug reactions, and drug interactions. Hopefully, this concise textbook is helpful at maintaining and enriching still existing pharmacology courses for the medical students and leads to their reinstitution when already dissipated.

I am aware of the cultural dimension of pharmacology, i.e., pharmacotherapy is performed differently in various countries. Therefore, I did not strictly adhere to clinical guidelines by particular learned societies but rather tried to explain the basic principles. Each professor is invited to adapt the principles laid out in this book to her/his particular situation in a given country. I also realize that it is impossible to generate a list of drugs that is unanimously approved by all pharmacologists. However, the proposed list of drugs covers all major indications except for tropical diseases. I plan to cover the latter topic in the next edition of the book.

After studying this book, the student should have a good overview on the most important drug classes and should be able to critically assess their value for the treatment of important diseases. I welcome any suggestions and critique to improve future editions of this book.

Roland Seifert
Hannover, Germany
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About the Author

Photo: Karin Kaiser, Hannover

Roland Seifert, MD, PhD

studied medicine at the Free University of Berlin (Germany) and obtained his PhD (habilitation degree) in Pharmacology and Toxicology in 1992 in the Pharmacology School of Günter Schultz. From 1995 to 1998, he was a postdoc at Stanford University, CA, USA, with Brian K. Kobilka. From 1998 to 2004, he was associate professor for Pharmacology and Toxicology at the University of Kansas, Lawrence, KS, USA. From 2004 to 2008, he served as director of the Institute of Pharmacology and Toxicology of the University of Regensburg (Germany). Since 2008, he has been the director of the Institute of Pharmacology and since 2019, additionally, director of the Research Core Unit Metabolomics at the Hannover Medical School (Germany). He is author of more than 240 peer-reviewed original papers and 40 reviews, predominantly in the fields of GPCRs and cyclic nucleotides. He is editor of several books, including two volumes of the *Handbook of Experimental Pharmacology*, and is the editor in chief of the oldest existing pharmacological journal, *Naunyn-Schmiedeberg's Archives of Pharmacology*. In 2018, he published his textbook *Basiswissen Pharmakologie* which he has now developed for an international audience. Seifert has been teaching all aspects of pharmacology to medical, pharmacy, and natural science students since 1986. He has received numerous teaching awards, both in the USA and Germany, for his continued outstanding teaching.

Abbreviations

AA	Arachidonic acid
AC	Adenylyl cyclase
ACE	Angiotensin-converting enzyme
ACEI	ACE inhibitor (ACE, angiotensin-converting enzyme)
ACh	Acetylcholine
AChE	Acetylcholinesterase
ACS	Acute coronary syndrome
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
ADHS	Attention deficit hyperactivity syndrome
ADME	Absorption, distribution, metabolization, elimination
ADPKD	Autosomal dominant polycystic kidney disease
ADR	Adverse drug reaction
AF	Atrial fibrillation
AICAR	5-aminoimidazole-4-carboxamide ribonucleotide
AMD	Age-related macular degeneration
AP	Angina pectoris
5-ASA	5-aminosalicylic acid
AR	Androgen receptor
ASA	Acetylsalicylic acid
AT_1R	Angiotensin-II receptor, subtype 1
ATO	Arsenic trioxide
ATRA	All-trans retinoic acid
$\alpha_x AR$	α-adrenoceptor (x, subtypes 1 and 2)
BBB	Blood-brain barrier
BK_2R	Bradykinin receptor, subtype 2
BP	Blood pressure
BPH	Benign prostatic hyperplasia
$\beta_x AR$	β-adrenoceptor (x, subtypes 1–3)
CAD	Cationic amphiphilic drug
CAH	Carbonic anhydrase
cAMP	Cyclic AMP (a second messenger)
CaSR	Calcium-sensing receptor
CB_1R	Cannabinoid receptor, subtype 1
CCB	Calcium channel blocker
CCK_2R	Cholecystokinin receptor, subtype 2
CCR5	CC chemokine receptor 5
CD	Crohn's disease
CDK	Cyclin-dependent kinase
CFTR	Cystic fibrosis transmembrane conductance regulator
cGMP	Cyclic GMP (a second messenger)
$[Ca^{2+}]_i$	Intracellular free calcium concentration
CGRP	Calcitonin gene-related peptide
CGRPR	Calcitonin gene-related peptide receptor
CHD	Coronary heart disease
CHF	Chronic heart failure
CKD	Chronic kidney disease
CO	Cardiac output
COMT	Catechol-O-methyltransferase
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase (subtypes 1 and 2)
CPB	Cardiopulmonary bypass
CTZ	Chemoreceptor trigger zone
CYP	Cytochrome-P_{450} isoenzyme (CYPXXX; subtype classification with combination uppercase letter - Arabic number - uppercase letter)
$CysLT_1R$	Leukotriene D_4 receptor
DA	Dopamine
DAT	Dopamine transporter
DM	Diabetes mellitus
DOAC	Direct-acting oral anticoagulant
DOR	δ-opioid receptor
DPP4	Dipeptidyl peptidase 4
D_2R-mGPCR antagonist	Antagonist at multiple GPCRs with preference for D_2R
D_xR	Dopamine receptor (x, subtypes 1–5)
DVT	Deep vein thrombosis
EC_{50} (ED_{50})	Concentration (dose) at which an agonist reaches 50% of its maximum effect
ECL	Enterochromaffin-like
ED	Erectile dysfunction
EE	Ethinylestradiol
EGF	Epidermal growth factor
EMB	Ethambutol
EPI	Epinephrine (adrenaline)

EPR	E-type prostaglandin receptor
EPS	Extrapyramidal symptom
ER	Estrogen receptor (subtypes α and β)
ET_AR	Endothelin receptor, subtype A
FI	Fusion inhibitor (HIV therapy)
FPR	F-type prostaglandin receptor
FSH	Follicle-stimulating hormone
5-FU	5-fluorouracil
GABA	γ-aminobutyric acid
$GABA_AR$	γ-aminobutyric acid receptor, subtype A
G-CSF	Granulocyte colony-stimulating factor
GC	Glucocorticoid
GCR	Glucocorticoid receptor
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
GLP-1R	Glucagon-like peptide 1 receptor
GPCR	G-protein-coupled receptor
GTN	Glyceryl trinitrate
$G_{(x)}$ protein	Heterotrimeric guanine nucleotide-binding protein (x, subtype s, i, o, or q)
HA	Histamine
HAART	Highly active antiretroviral therapy
HCMV	Human cytomegalovirus
HCN4	Hyperpolarization-activated cyclic nucleotide-gated channel 4
HCV	Hepatitis C virus
HDC	Histone deacetylase
HER2	Human epithelial growth factor receptor 2
HERG channel	Human ether-à-go-go-related gene channel
HIT	Heparin-induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG CoA reductase	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HR	Heart rate
HRT	Hormone replacement therapy
HSV	Herpes simplex virus
5-HT	5-hydroxytryptamine (5-HT, serotonin)
$5\text{-}HT_xR$	5-hydroxytryptamine (5-HT, serotonin) receptor (x, subtypes 1–7)
H_xR	Histamine receptor (x, subtypes 1–4)
I	Inhibitor (of an enzyme or of a cytokine)
IC_{50} (ID_{50})	Concentration (dose) at which an antagonist or an enzyme inhibitor reaches 50% of its maximum inhibition
IGCR	Inhaled glucocorticoid receptor agonist
IFN	Interferon
IL-X	Interleukin; X designates the specific interleukin
i.m.	Intramuscular
INH	Isoniazid
INI	Integrase inhibitor (HIV therapy)
INN	International nonproprietary name
INR	International normalized ratio (this parameter is used to adjust VKA therapy)
IOP	Intraocular pressure
IPR	Prostacyclin (PGI_2) receptor
IUD	Intrauterine device
i.v.	Intravenous
KOR	κ-opioid receptor
LABA	Long-acting β_2-adrenoceptor agonist (controller)
LAMA	Long-acting M_3R antagonist
LH	Luteinizing hormone
LMWH	Low-molecular-weight heparin
LOX	Lipoxygenase
LSD	Lysergic acid diethylamide
LT	Leukotriene
LTRA	Leukotriene receptor antagonist
MAO	Monoamine oxidase (subtypes A and B)
MAOI	Monoamine oxidase inhibitor
MCP	Metoclopramide
MCR	Mineralocorticoid receptor
MCRA	Mineralocorticoid receptor antagonist
mGPCR antagonist	Antagonist at multiple GPCRs
MHV	Mechanical heart valve
MI	Myocardial infarction
MOR	μ-opioid receptor

6-MP	6-mercaptopurine
MRP	Multidrug resistance protein
MRSA	Multidrug-resistant *Staphylococcus aureus*
MS	Multiple sclerosis
mTOR	Mechanistic target of rapamycin
MTX	Methotrexate
M_xR	Muscarinic acetylcholine receptor (x, subtypes 1–5)
nAChR	Nicotinic acetylcholine receptor
NE	Norepinephrine (noradrenaline)
NE/5-HT enhancers	Drugs enhancing the effects of norepinephrine and serotonin
NEP	Neprilysin
NET	Norepinephrine transporter
NIPE	Neuron inhibitor with pleiotropic effects
NK_1R	Neurokinin receptor, subtype 1
NMDA	N-methyl-D-aspartate
NNRTI	Non-nucleoside reverse transcriptase inhibitor (HIV therapy)
NO	Nitric oxide
NPC1L1	*Niemann-Pick C1-like protein*
NR	Nuclear receptor
NRTI	Nucleoside reverse transcriptase inhibitor (HIV therapy)
NSMRI	Nonselective monoamine re-uptake inhibitor
NT	Neurotransmitter
OAT	Organic anion transporter
OR	Opioid receptor (subtypes M (μ), D (δ), and K (κ))
OTC	Over the counter
PAD	Peripheral arterial disease
PAH	Pulmonary arterial hypertension
PAI	Platelet aggregation inhibitor
PAR1	Protease-activated receptor 1 (thrombin receptor)
PARP-1	Poly(ADP ribose) polymerase 1
PCSK9	Proprotein convertase subtilisin/kexin type 9
PDE	Phosphodiesterase (subtypes 3, 4, and 5 are clinically important)
PE	Pulmonary embolism
PI	Protease inhibitor (HIV and HCV therapy)
PG	Prostaglandin
PK	Protein kinase
PLA_2	Phospholipase A_2
PLC	Phospholipase C
p-mGPCR antagonist	Antagonist at multiple GPCRs with pleiotropic effects
PML	Progressive multifocal leukoencephalopathy
p.o.	Per os (peroral)
PP	Proton pump
PPAR	Peroxisome proliferator-activated receptor (receptor subtypes α and γ)
PPI	Proton pump inhibitor
PR	Progesterone receptor
PTH	Parathyroid hormone
PTHR	Parathyroid hormone receptor
PUD	Peptic ulcer disease
$P2Y_{12}R$	Purinergic receptor for ADP predominantly expressed on platelets
PZA	Pyrazinamide
R	Receptor
RAAS	Renin-angiotensin-aldosterone system
Raf	Rapidly accelerated fibrosarcoma protein kinase
RANK	Receptor activator of nuclear factor κB
RANKL	Receptor activator of nuclear factor-κB ligand
RMP	Rifampicin
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
SABA	Short-acting β_2AR agonist (reliever)
SAMA	Short-acting M_3R antagonist
s.c.	Subcutaneous
SCB	Sodium channel blocker
SERM	Selective estrogen receptor modulator
SERT	Serotonin transporter
sGC	Soluble guanylyl cyclase
SGLT-2	Sodium/glucose cotransporter 2
SJS	Stevens-Johnson syndrome
SM	Streptomycin
SNP	Sodium nitroprusside
s/p	Status post
$S1P_1R$	Sphingosine-1-phosphate receptor, subtype 1

SSNRI	Selective 5-HT/NE re-uptake inhibitor
SSRI	Selective 5-HT re-uptake inhibitor
SVR	Systemic vascular resistance
t ½	Half-life
T3	Liothyronine
T4	Levothyroxine
TB	Tuberculosis
TD_{50}	Dose at which a drug (active component) reaches 50% of its maximum toxic effect
TDM	Therapeutic drug monitoring
TdP	*Torsade-de-pointes* arrhythmia
TEN	Toxic epidermal necrolysis
THC	Tetrahydrocannabinol
TIVA	Total intravenous anesthesia
TK	Tyrosine kinase
TMP	Trimethoprim
TNF	Tumor necrosis factor
TOPO	Topoisomerase
TPO	Thyroid peroxidase
TPR	Thromboxane A_2 (TXA_2) receptor
TSH	Thyroid-stimulating hormone
TX	Thromboxane
UC	Ulcerative colitis
UFH	Unfractionated heparin
URAT1	Urate transporter 1
VEGF	Vascular endothelial growth factor
VKA	Vitamin K antagonist
V_2R	Vasopressin receptor, subtype 2
VT	Ventricular tachycardia
VZV	Varicella zoster virus
XO	Xanthine oxidase

General Principles

Contents

Introduction and Pharmacodynamics

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1

Pharmacologically active substances comprise drugs and poisons. Drugs possess therapeutically beneficial, and poisons possess deleterious effects. Drugs should be named by their INNs and not by their brand names. There are substantial cultural differences in the use of a given drug in various countries. Drugs should be classified according to their mechanism of action, and traditional slang terms should be avoided. Medicines are pharmaceutical preparations of drugs for use in humans. Development of a drug into a medicine comprises preclinical and clinical development. The latter is divided into three phases. Pharmacodynamics analyzes the effects of pharmacologically active substances on the human organism. Receptors, enzymes, ion channels, and transporters are the most important target classes for drugs. Receptors are divided into GPCRs, ligand-gated ion channels, TK-linked receptors, and NRs. Receptors are activated by agonists. Antagonists block the effects of agonists. The function of enzymes and transporters is reduced by inhibitors. Ion channel function is reduced by blockers and increased by activators. Complete concentration-response relationships are required to assess the effects of drugs with the parameters EC_{50}, IC_{50}, and intrinsic activity. The therapeutic index is a measure for the safety of a drug. Many drugs have a small therapeutic index and should, therefore, be dosed prudently. Some drugs with a small therapeutic index are even available OTC.

Key Points

1. Drugs have beneficial effects; poisons have deleterious effects.
2. The classification of a pharmacologically active substance as drug or poison depends on the specific pathophysiological context.
3. INNs of drugs should be used to avoid dependence on brand names that often have a suggestive character.
4. The word ending of an INN often provides information on the mechanism of action of a drug.
5. Slang names for drug classes such as "betablocker" or "antihistamine" should be strictly avoided.
6. Many traditional names of drug classes such as "DMARDs," "NSAIDs," "antidepressants," "antiepileptics," and "antipsychotics" lack scientific rigor and focus on a particular clinical use without being comprehensive.
7. Whenever possible, drugs should be classified according to their mechanism of action or, where more appropriate, according to their chemical properties.
8. The classification of drugs according to their mechanism of action is neutral and allows for expansion of indications without irritation or bias.
9. A mechanism-based drug nomenclature improves precise pharmacotherapy and drug safety.
10. The indications of many drug classes, specifically psychiatric drugs, have expanded substantially over the past 10 years.
11. Globally, there are substantial cultural differences in the use of individual drugs.
12. Development of a drug comprises a preclinical and clinical phase.
13. In the clinical development of drugs, it is critical to include a standard therapy as reference whenever possible.
14. Pharmacodynamics analyzes the effects of pharmacologically active substances on the human organism.
15. Receptors, enzymes, transporters, and ion channels are the most important target classes for drugs.
16. Potency designates the concentration of a drug at which its stimulatory or inhibitory effect is half-maximal.
17. Intrinsic activity describes the maximum effect of an agonist at a receptor.
18. Partial agonists possess a lower intrinsic activity than agonists; antagonists possess no intrinsic activity.
19. Long-term therapy with GPCR agonists can result in tolerance due to receptor desensitization.
20. The therapeutic index is a measure for the safety of a drug.
21. In order to ensure therapeutic efficacy, in life-threatening diseases, a smaller

therapeutic index must be accepted than in non-life-threatening diseases.
22. Some drugs with a small therapeutic index are available OTC.
23. Accordingly, even OTC drugs can cause serious intoxications when abused.

1.1 Drugs and Poisons

Pharmacology is the science that analyzes the interactions of substances with the human organism. Pharmacodynamics describes the effects of substances on the organism, whereas pharmacokinetics analyzes the effects of the organism on substances and the path of drugs through the organism (see ▶ Chap. 2). Pharmacology is situated at the interface between physiology and pathophysiology. Pharmacology aims at curing diseases or at least mitigating disease symptoms on the basis of pathophysiologically validated concepts. For certain diseases such as hypertension (see ▶ Chap. 15), very effective and economical pharmacological treatments are available. In contrast, other diseases such as arrhythmias are much more difficult to treat pharmacologically (see ▶ Chap. 17). Accordingly, the focus for such diseases is to avoid their occurrence and particularly to avoid drugs causing arrhythmias.

Pharmacologically active substances are all chemical compounds that influence body functions. The term "pharmacologically active substance" makes no predictions about the benefit or harm of its effects. Drugs possess beneficial (therapeutic) effects, whereas poisons have deleterious (toxic) effects. The definition of a pharmacologically active substance as drug or poison depends on the dose, mode of application, and the clinical situation.

As an example, if a small child accidentally ingests fruits from the deadly nightshade which contains atropine in large amounts, a muscarinic syndrome develops (see ▶ Chaps. 4 and 5). In this situation, atropine is a poison. In contrast, for bradycardia during surgery, atropine is a drug. In patients suffering from depression, NSMRIs can be mood-lifting and increase motivation. However, when large amounts of an NSMRI are ingested suicidally, the drug acts as poison and can induce severe hypotension due to M_xR and α_1AR antagonism (see ▶ Chaps. 4 and 28).

1.2 Drugs and Medicines

Medicines are pharmaceutical preparations of drugs for use in humans. In addition to the drug, a medicine also contains pharmaceutical excipients that keep the drug in solution and accelerate or delay its absorption (controlled release formulations). Medicines can cause allergic reactions (see ▶ Chaps. 3). Medicines comprise non-coated and coated tablets for oral administration, suppositories for rectal administration, transdermal systems for controlled release of a drug, and solutions for i.v., s.c., and i.m. injection, capsules for sublingual administration ensuring rapid systemic absorption and ointments, creams, eye drops, nose drops and sprays for local administration.

Medicines without drug can exert therapeutic effects as well, specifically in situations with a psychological component. Such medicines are referred to as placebos. In headache, the response rate of placebos ranges between 30 and 70% (see ▶ Chap. 10), for GI disturbances between 20 and 60% (see ▶ Chap. 12), and for insomnia between 50 and 80% (see ▶ Chap. 25). The effects of placebos are due to the suggestive power of the physician, expectations of the patient, and behavioral conditioning. Placebos can also exhibit ADRs (nocebo effect). Sleepiness, abdominal pain, and headache are typical nocebo effects and occur in up to 50% of all patients treated with placebos.

The effects of a given medicine in humans are not always identical but may differ substantially, depending on a multitude of factors. Ethnicity, sex, age, reproductive function, dietary habits, comorbidities, ethanol consumption, liver and kidney function, hormonal status, co-medication with other drugs, and genetic polymorphisms of receptors and enzymes all affect drug efficacy. While it is impossible to discuss all these variables systematically within the constraints of this basic text, important examples where these factors act will be discussed where appropriate.

1.3 International Nonproprietary Names (INN) Versus Brand Names

The international nonproprietary names (INNs) are the universal drug names. These names are used globally. There are only few exceptions from this rule. For example, in the USA and the UK, the β_2AR