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Basic Knowledge of Pharmacology

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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 re-institution 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.

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April 2019

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About the Author



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Abbreviations

AA	Arachidonic acid	CFTR	Cystic fibrosis transmembrane conductance regulator
AC	Adenylyl cyclase	cGMP	Cyclic GMP (a second messenger)
ACE	Angiotensin-converting enzyme	[Ca²⁺]_i	Intracellular free calcium concentration
ACEI	ACE inhibitor (ACE, angiotensin-converting enzyme)	CGRP	Calcitonin gene-related peptide
ACh	Acetylcholine	CGRPR	Calcitonin gene-related peptide receptor
AChE	Acetylcholinesterase	CHD	Coronary heart disease
ACS	Acute coronary syndrome	CHF	Chronic heart failure
ACTH	Adrenocorticotrophic hormone	CKD	Chronic kidney disease
AD	Alzheimer's disease	CO	Cardiac output
ADHS	Attention deficit hyperactivity syndrome	COMT	Catechol-O-methyltransferase
ADME	Absorption, distribution, metabolism, elimination	COPD	Chronic obstructive pulmonary disease
ADPKD	Autosomal dominant polycystic kidney disease	COX	Cyclooxygenase (subtypes 1 and 2)
ADR	Adverse drug reaction	CPB	Cardiopulmonary bypass
AF	Atrial fibrillation	CTZ	Chemoreceptor trigger zone
AICAR	5-aminoimidazole-4-carboxamide ribonucleotide	CYP	Cytochrome-P ₄₅₀ isoenzyme (CYPXXX; subtype classification with combination uppercase letter - Arabic number - uppercase letter)
AMD	Age-related macular degeneration	CysLT₁R	Leukotriene D ₄ receptor
AP	Angina pectoris	DA	Dopamine
5-ASA	5-aminosalicylic acid	DAT	Dopamine transporter
AR	Androgen receptor	DM	Diabetes mellitus
ASA	Acetylsalicylic acid	DOAC	Direct-acting oral anticoagulant
AT₁R	Angiotensin-II receptor, subtype 1	DOR	δ-opioid receptor
ATO	Arsenic trioxide	DPP4	Dipeptidyl peptidase 4
ATRA	All-trans retinoic acid	D₂R-mGPCR antagonist	Antagonist at multiple GPCRs with preference for D ₂ R
α_xAR	α-adrenoceptor (x, subtypes 1 and 2)	D_xR	Dopamine receptor (x, subtypes 1–5)
BBB	Blood-brain barrier	DVT	Deep vein thrombosis
BK₂R	Bradykinin receptor, subtype 2	EC₅₀ (ED₅₀)	Concentration (dose) at which an agonist reaches 50% of its maximum effect
BP	Blood pressure	ECL	Enterochromaffin-like
BPH	Benign prostatic hyperplasia	ED	Erectile dysfunction
β_xAR	β-adrenoceptor (x, subtypes 1–3)	EE	Ethinylestradiol
CAD	Cationic amphiphilic drug	EGF	Epidermal growth factor
CAH	Carbonic anhydrase	EMB	Ethambutol
cAMP	Cyclic AMP (a second messenger)	EPI	Epinephrine (adrenaline)
CaSR	Calcium-sensing receptor		
CB₁R	Cannabinoid receptor, subtype 1		
CCB	Calcium channel blocker		
CCK₂R	Cholecystokinin receptor, subtype 2		
CCRS	CC chemokine receptor 5		
CD	Crohn's disease		
CDK	Cyclin-dependent kinase		

EPR	E-type prostaglandin receptor	5-HT_xR	5-hydroxytryptamine (5-HT, serotonin) receptor (x, subtypes 1–7)
EPS	Extrapyramidal symptom	H_xR	Histamine receptor (x, subtypes 1–4)
ER	Estrogen receptor (subtypes α and β)	I	Inhibitor (of an enzyme or of a cytokine)
ET_AR	Endothelin receptor, subtype A	IC₅₀ (ID₅₀)	Concentration (dose) at which an antagonist or an enzyme inhibitor reaches 50% of its maximum inhibition
FI	Fusion inhibitor (HIV therapy)	IGCR	Inhaled glucocorticoid receptor agonist
FPR	F-type prostaglandin receptor	IFN	Interferon
FSH	Follicle-stimulating hormone	IL-X	Interleukin; X designates the specific interleukin
5-FU	5-fluorouracil	i.m.	Intramuscular
GABA	γ -aminobutyric acid	INH	Isoniazid
GABA_AR	γ -aminobutyric acid receptor, subtype A	INI	Integrase inhibitor (HIV therapy)
G-CSF	Granulocyte colony-stimulating factor	INN	International nonproprietary name
GC	Glucocorticoid	INR	International normalized ratio (this parameter is used to adjust VKA therapy)
GCR	Glucocorticoid receptor	IOP	Intraocular pressure
GERD	Gastroesophageal reflux disease	IPR	Prostacyclin (PGI ₂) receptor
GFR	Glomerular filtration rate	IUD	Intrauterine device
GI	Gastrointestinal	i.v.	Intravenous
GLP-1	Glucagon-like peptide 1	KOR	κ -opioid receptor
GLP-1R	Glucagon-like peptide 1 receptor	LABA	Long-acting β_2 -adrenoceptor agonist (controller)
GPCR	G-protein-coupled receptor	LAMA	Long-acting M ₃ R antagonist
GTN	Glyceryl trinitrate	LH	Luteinizing hormone
G_(x) protein	Heterotrimeric guanine nucleotide-binding protein (x, subtype s, i, o, or q)	LMWH	Low-molecular-weight heparin
HA	Histamine	LOX	Lipoxygenase
HAART	Highly active antiretroviral therapy	LSD	Lysergic acid diethylamide
HCMV	Human cytomegalovirus	LT	Leukotriene
HCN4	Hyperpolarization-activated cyclic nucleotide-gated channel 4	LTRA	Leukotriene receptor antagonist
HCV	Hepatitis C virus	MAO	Monoamine oxidase (subtypes A and B)
HDC	Histone deacetylase	MAOI	Monoamine oxidase inhibitor
HER2	Human epithelial growth factor receptor 2	MCP	Metoclopramide
HERG channel	Human ether-à-go-go-related gene channel	MCR	Mineralocorticoid receptor
HIT	Heparin-induced thrombocytopenia	MCRA	Mineralocorticoid receptor antagonist
HIV	Human immunodeficiency virus	mGPCR antagonist	Antagonist at multiple GPCRs
HLA	Human leukocyte antigen	MHV	Mechanical heart valve
HMG CoA reductase	3-hydroxy-3-methylglutaryl-coenzyme A reductase	MI	Myocardial infarction
HR	Heart rate	MOR	μ -opioid receptor
HRT	Hormone replacement therapy		
HSV	Herpes simplex virus		
5-HT	5-hydroxytryptamine (5-HT, serotonin)		

Abbreviations

6-MP	6-mercaptopurine	PK	Protein kinase
MRP	Multidrug resistance protein	PLA₂	Phospholipase A ₂
MRSA	Multidrug-resistant <i>Staphylococcus aureus</i>	PLC	Phospholipase C
MS	Multiple sclerosis	p-mGPCR antagonist	Antagonist at multiple GPCRs with pleiotropic effects
mTOR	Mechanistic target of rapamycin	PML	Progressive multifocal leukoencephalopathy
MTX	Methotrexate	p.o.	Per os (peroral)
M_xR	Muscarinic acetylcholine receptor (x, subtypes 1–5)	PP	Proton pump
nAChR	Nicotinic acetylcholine receptor	PPAR	Peroxisome proliferator-activated receptor (receptor subtypes α and γ)
NE	Norepinephrine (noradrenaline)	PPI	Proton pump inhibitor
NE/5-HT enhancers	Drugs enhancing the effects of norepinephrine and serotonin	PR	Progesterone receptor
NEP	Neprilysin	PTH	Parathyroid hormone
NET	Norepinephrine transporter	PTHR	Parathyroid hormone receptor
NIPE	Neuron inhibitor with pleiotropic effects	PUD	Peptic ulcer disease
NK₁R	Neurokinin receptor, subtype 1	P2Y₁₂R	Purinergic receptor for ADP predominantly expressed on platelets
NMDA	N-methyl-D-aspartate	PZA	Pyrazinamide
NNRTI	Non-nucleoside reverse transcriptase inhibitor (HIV therapy)	R	Receptor
NO	Nitric oxide	RAAS	Renin-angiotensin-aldosterone system
NPC1L1	<i>Niemann-Pick C1-like protein</i>	Raf	Rapidly accelerated fibrosarcoma protein kinase
NR	Nuclear receptor	RANK	Receptor activator of nuclear factor κB
NRTI	Nucleoside reverse transcriptase inhibitor (HIV therapy)	RANKL	Receptor activator of nuclear factor-κB ligand
NSMRI	Nonselective monoamine re-uptake inhibitor	RMP	Rifampicin
NT	Neurotransmitter	ROS	Reactive oxygen species
OAT	Organic anion transporter	RTK	Receptor tyrosine kinase
OR	Opioid receptor (subtypes M (μ), D (δ), and K (κ))	SABA	Short-acting β ₂ AR agonist (reliever)
OTC	Over the counter	SAMA	Short-acting M ₃ R antagonist
PAD	Peripheral arterial disease	s.c.	Subcutaneous
PAH	Pulmonary arterial hypertension	SCB	Sodium channel blocker
PAI	Platelet aggregation inhibitor	SERM	Selective estrogen receptor modulator
PAR1	Protease-activated receptor 1 (thrombin receptor)	SERT	Serotonin transporter
PARP-1	Poly(ADP ribose) polymerase 1	sGC	Soluble guanylyl cyclase
PCSK9	Proprotein convertase subtilisin/kexin type 9	SGLT-2	Sodium/glucose cotransporter 2
PDE	Phosphodiesterase (subtypes 3, 4, and 5 are clinically important)	SJS	Stevens-Johnson syndrome
PE	Pulmonary embolism	SM	Streptomycin
PI	Protease inhibitor (HIV and HCV therapy)	SNP	Sodium nitroprusside
PG	Prostaglandin	s/p	Status post
		S1P₁R	Sphingosine-1-phosphate receptor, subtype 1

SSNRI	Selective 5-HT/NE re-uptake inhibitor	TNF	Tumor necrosis factor
SSRI	Selective 5-HT re-uptake inhibitor	TOPO	Topoisomerase
SVR	Systemic vascular resistance	TPO	Thyroid peroxidase
t_{1/2}	Half-life	TPR	Thromboxane A ₂ (TXA ₂) receptor
T3	Liothyronine	TSH	Thyroid-stimulating hormone
T4	Levothyroxine	TX	Thromboxane
TB	Tuberculosis	UC	Ulcerative colitis
TD₅₀	Dose at which a drug (active component) reaches 50% of its maximum toxic effect	UFH	Unfractionated heparin
TDM	Therapeutic drug monitoring	URAT1	Urate transporter 1
TdP	<i>Torsade-de-pointes</i> arrhythmia	VEGF	Vascular endothelial growth factor
TEN	Toxic epidermal necrolysis	VKA	Vitamin K antagonist
THC	Tetrahydrocannabinol	V₂R	Vasopressin receptor, subtype 2
TIVA	Total intravenous anesthesia	VT	Ventricular tachycardia
TK	Tyrosine kinase	VZV	Varicella zoster virus
TMP	Trimethoprim	XO	Xanthine oxidase

General Principles

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Introduction and Pharmacodynamics

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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