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RANG AND DALE'S Pharmacology

H. P. RANG • M. M. DALE • J. M. RITTER • R. J. FLOWER • G. HENDERSON

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RANG AND DALE'S

Pharmacology

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Cover image shows white blood cells emigrating from blood vessels.

The inner surface of blood vessels are lined with endothelial cells which express a protein called PECAM-1 at the junction between cells, and less strongly on the cell body. This protein was labelled red with a fluorescently tagged antibody, and genetic modification was used to make the white blood cells (leukocytes) express green fluorescent protein. These can be seen sticking to the endothelial cells, and beginning to transmigrate through the blood vessel wall in response to an inflammatory stimulus.

The image was captured by confocal microscopy with laser excitation of the green and red fluorescent labels. A series of flat images through the vessel were taken, and these slices were reconstructed to make a 3D object.

Image generated by S. Nourshagh, A. Woodfin and M. Benoit-Voisin (William Harvey Research Institute, London).

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Rang and Dale's Pharmacology 7th Edition Preface

In this edition, as in its predecessors, we set out not just to describe what drugs do but to emphasise the mechanisms by which they act. This entails analysis not only at the cellular and molecular level, where knowledge and techniques are advancing rapidly, but also at the level of physiological mechanisms and pathological disturbances. Pharmacology has its roots in therapeutics, where the aim is to ameliorate the effects of disease, so we have attempted to make the link between effects at the molecular and cellular level and the range of beneficial and adverse effects that humans experience when drugs are used for therapeutic or other reasons. Therapeutic agents have a high rate of obsolescence, and new ones appear each year. An appreciation of the mechanisms of action of the class of drugs to which a new agent belongs provides a good starting point for understanding and using a new compound intelligently.

Pharmacology is a lively scientific discipline in its own right, with an importance beyond that of providing a basis for the use of drugs in therapy, and we aim to provide a good background, not only for future doctors but also for scientists and practitioners of other disciplines. We have therefore, where appropriate, described how drugs are used as probes for elucidating cellular and physiological functions, even when the compounds have no clinical use.

Names of drugs and related chemicals are established through usage and sometimes there is more than one name in common use. For prescribing purposes, it is important to use standard names, and we follow as far as possible the World Health Organization's list of recommended international non-proprietary names (rINN). Sometimes these conflict with the familiar names of drugs (e.g amphetamine becomes amfetamine in the rINN list, and the endogenous mediator prostaglandin I_2 – the standard name in the scientific literature - becomes 'epoprostenol'– a name unfamiliar to most scientists – in the rINN list. In general, we use rINN names as far as possible in the context of therapeutic use, but often use the common name in describing mediators and familiar drugs. Sometimes English and American usage varies (as with adrenaline/epinephrine and noradrenaline/norepinephrine). Adrenaline and noradrenaline are the official names in EU member states and relate clearly to terms such as 'noradrenergic', 'adrenoceptor' and 'adrenal gland' and we prefer them for these reasons.

Drug action can be understood only in the context of what else is happening in the body. So at the beginning of most chapters, we briefly discuss the physiological and biochemical processes relevant to the action of the drugs described in that chapter. We have routinely included the chemical structures of drugs, but have only done so where this information helps in understanding their pharmacological and pharmacokinetic characteristics.

The overall organization of the book has been retained, with sections covering: (1) the general principles of drug action; (2) the chemical mediators and cellular mechanisms with which drugs interact in producing their therapeutic effects; (3) the action of drugs on specific organ systems; (4) the action of drugs on the nervous system; (5) the action of drugs used to treat infectious diseases and cancer; (6) a range of special topics such as individual variation in drug effects, adverse effects, non-medical uses of drugs, etc. This organization reflects our belief that drug action needs to be understood, not as a mere description of the effects of individual drugs and their uses, but as a chemical intervention that perturbs the complex network of chemical and cellular signaling that underlies the function of any living organism. In addition to updating all of the chapters, we have, within this general plan, reorganized the text in various ways, to keep abreast of modern developments:

- A new chapter (Ch. 6) on host defense mechanisms has been included in the section on cellular mechanisms.
- Pharmacogenetics, an increasingly important topic for prescribers, is treated in a separate chapter (Ch. 11).
- A new chapter on the pharmacology of purines (Ch. 16) has been included.
- A new chapter (Ch. 17) on local hormones and other mediators involved in inflammatory and immune responses has been included in the section on chemical mediators, with information on immunosuppressant and anti-inflammatory drugs (Ch. 26) presented separately
- Several chapters in Section 3 (Drugs affecting major organ systems) and Section 4 (Nervous system) have been substantially revised and reorganized to include recent developments.

Despite the fact that pharmacology, like other branches of biomedical science, advances steadily, with the acquisition of new information, the development of new concepts and the introduction of new drugs for clinical use, we have avoided making the 7th edition any longer than its predecessor. We have cut out some material, including drugs that have become obsolete, and theories that have had their day, and have made extensive use of small print text to cover more specialized and speculative information that is not essential to understanding the key message, but will, we hope, be helpful to students seeking to go into greater depth.

In selecting new material for inclusion, we have taken into account not only new agents but also recent extensions of basic knowledge that presage further drug development. And where possible, we have given a brief outline of new treatments in the pipeline.

The References and Further Reading sections at the end of each chapter have been updated throughout, and include reliable websites. Short descriptions have been added to most references, summarising the main aspects covered. While the lists are by no means exhaustive, we hope that they will be helpful as a way in to the literature for students wanting to go into greater depth.

We are grateful to the readers who have taken the trouble to write to us with constructive comments and suggestions about the 6th edition. We have done our best to incorporate these. Comments on the new edition will be welcome.

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Abbreviations and Acronyms

α-Me-5-HT α-methyl 5-hydroxytrypamine
α-MSH α-melanocyte-stimulating hormone
12-*S*-HETE 12-*S*-hydroxyeicosatetraenoic acid
2-AG 2-arachidonoyl glycerol
2-Me-5-HT 2-methyl-5-hydroxytrypamine
4S Scandinavian Simvastatin Survival Study
5-CT 5-carboxamidotryptamine
5-HIAA 5-hydroxyindoleacetic acid
5-HT 5-hydroxytryptamine [serotonin]
8-OH-DPAT 8-hydroxy-2-(di-*n*-propylamino) tetraline
AA arachidonic acid
AC adenylyl cyclase
ACAT acyl coenzyme A: cholesterol acyltransferase
AcCoA acetyl coenzyme A
ACE angiotensin-converting enzyme
ACh acetylcholine
AChE acetylcholinesterase
ACTH adrenocorticotrophic hormone
AD Alzheimer's disease
ADH antidiuretic hormone
ADHD attention-deficit hyperactivity disorder
ADMA asymmetric dimethylarginine
ADME absorption, distribution, metabolism and elimination [studies]
ado-B12 5′-deoxyadenosylcobalamin
ADP adenosine diphosphate
AF1 activation function 1
AF2 activation function 2
AGEPC acetyl-glyceryl-ether-phosphorylcholine
AGRP agouti-related protein
Ah aromatic hydrocarbon
AIDS acquired immunodeficiency syndrome
AIF apoptotic initiating factor
ALA δ-amino laevulinic acid
ALDH aldehyde dehydrogenase
AMP adenosine monophosphate
AMPA α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid
ANF atrial natriuretic factor
ANP atrial natriuretic peptide
AP adapter protein
Apaf-1 apoptotic protease-activating factor-1
APC antigen-presenting cell
APP amyloid precursor protein
APTT activated partial thromboplastin time
AR aldehyde reductase; androgen receptor
Arg arginine
ARND alcohol-related neurodevelopmental disorder
ASCI ATP-sensitive Ca^{2+}-insensitive
ASCOT Anglo-Scandinavian Cardiac Outcomes Trial
ASIC acid-sensing ion channel
AT angiotensin
AT_1 angiotensin II receptor subtype 1
AT_2 angiotensin II receptor subtype 2
ATIII antithrombin III
ATP adenosine triphosphate
AUC area under the curve
AV atrioventricular
AZT zidovudine
BARK β-adrenoreceptor kinase
BDNF brain-derived neurotrophic factor
B_{max} binding capacity
BMI body mass index
BMPR-2 bone morphogenetic protein receptor type 2
BNP B-type natriuretic peptide
BSE bovine spongiform encephalopathy
BuChE butyrylcholinesterase
CaC calcium channel
CAD coronary artery disease
cADPR cyclic ADP-ribose
CaM calmodulin
cAMP cyclic 3′,5′-adenosine monophosphate
CAR constitutive androstane receptor
CARE Cholesterol and Recurrent Events [trial]
CAT choline acetyltransferase

CBG corticosteroid-binding globulin
CCK cholecystokinin
cdk cyclin-dependent kinase
cDNA circular deoxyribonucleic acid
CETP cholesteryl ester transfer protein
CFTR cystic fibrosis transport [transmembrane conductance] regulator
cGMP cyclic guanosine monophosphate
CGRP calcitonin gene-related peptide
ChE cholinesterase
CHO Chinese hamster ovary [cell]
CICR calcium-induced calcium release
CIP cdk inhibitory protein
CJD Creutzfeldt–Jakob disease
CL total clearance of a drug
CNP C-natriuretic peptide
CNS central nervous system
CO carbon monoxide
CoA coenzyme A
COMT catechol-*O*-methyl transferase
COPD chronic obstructive pulmonary disease
COX cyclo-oxygenase
CREB cAMP response element-binding protein
CRF corticotrophin-releasing factor
CRH corticotrophin-releasing hormone
CRLR calcitonin receptor-like receptor
CSF cerebrospinal fluid; colony-stimulating factor
C_{ss} steady-state plasma concentration
CTL cytotoxic T lymphocyte
CTZ chemoreceptor trigger zone
CYP cytochrome P450 [system]
DAAO D-amino acid oxidase
DAG diacylglycerol
DAGL diacylglycerol lipase
DAT dopamine transporter
DBH dopamine-β-hydroxylase
DDAH dimethylarginine dimethylamino hydrolase
DHFR dihydrofolate reductase
DHMA 3,4-dihydroxymandelic acid
DHPEG 3,4-dihydroxyphenylglycol
DIT di-iodotyrosine
DMARD disease-modifying antirheumatic drug
DMPP dimethylphenylpiperazinium
DNA deoxyribonucleic acid
DOH oxidised [hydroxylated] drug
DOPA dihydroxyphenylalanine
DOPAC dihydroxyphenylacetic acid
DSI depolarisation-induced suppression of inhibition
DTMP 2-deoxythymidylate
DUMP 2-deoxyuridylate
EAA excitatory amino acid
EC_{50}/ED_{50} concentration/dose effective in 50% of the population
ECG electrocardiogram
ECM extracellular matrix
ECP eosinophil cationic protein
ECT electroconvulsive therapy
EDHF endothelium-derived hyperpolarising factor
EDRF endothelium-derived relaxing factor
EEG electroencephalography
EET epoxyeicosatetraenoic acid
EGF epidermal growth factor
EG-VEGF endocrine gland-derived vascular endothelial growth factor
E_{max} maximal response that a drug can produce
EMBP eosinophil major basic protein
EMT endocannabinoid membrane transporter
ENaC epithelial sodium channel
eNOS endothelial nitric oxide synthase [NOS-III]
epp endplate potential
EPS extrapyramidal side effects
epsp excitatory postsynaptic potential
ER endoplasmic reticulum; (o)estrogen receptor
FA kinase focal adhesion kinase
FAAH fatty acid amide hydrolase
FAD flavin adenine dinucleotide
FAS fetal alcohol syndrome
FDUMP fluorodeoxyuridine monophosphate
Fe^{2+} ferrous iron
Fe^{3+} ferric iron
FeO^{3+} ferric oxene
FEV_1 forced expiratory volume in 1 second
FGF fibroblast growth factor
FH_2 dihydrofolate
FH_4 tetrahydrofolate
FKBP FK-binding protein
FLAP five-lipoxygenase activating protein
FMN flavin mononucleotide

formyl-FH_4 formyl tetrahydrofolate
FSH follicle-stimulating hormone
FXR farnesoid [bile acid] receptor
G6PD glucose 6-phosphate dehydrogenase
GABA gamma-aminobutyric acid
GAD glutamic acid decarboxylase
GC guanylyl cyclase
G-CSF granulocyte colony-stimulating factor
GDP guanosine diphosphate
GFR glomerular filtration rate
GH growth hormone
GHB γ-hydroxybutyrate
GHRF growth hormone-releasing factor
GHRH growth hormone-releasing hormone
GI gastrointestinal
GIP gastric inhibitory polypeptide
GIRK G-protein-sensitive inward-rectifying potassium [channel]
GIT gastrointestinal tract
Gla γ-carboxylated glutamic acid
GLP glucagon-like peptide
Glu glutamic acid
GM-CSF granulocyte–macrophage colony-stimulating factor
GnRH gonadotrophin-releasing hormone
GP glycoprotein
GPCR G-protein-coupled receptor
GPL glycerophospholipid
GR glucocorticoid receptor
GRE glucocorticoid response element
GRK GPCR kinase
GSH glutathione
GSSG glutathione, oxidised
GTP guanosine triphosphate
H_2O_2 hydrogen peroxide
HAART highly active antiretroviral therapy
hCG human chorionic gonadotrophin
HCl hydrochloric acid
HDAC histone deacetylase
HDL high-density lipoprotein
HDL-C high-density-lipoprotein cholesterol
HER2 human epidermal growth factor receptor 2
HERG human ether-a-go-go related gene
HETE hydroxyeicosatetraenoic acid
hGH human growth hormone
HIT heparin-induced thrombocytopenia
HIV human immunodeficiency virus
HLA histocompatibility antigen
HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A
HnRNA heterologous nuclear RNA
HPA hypothalamic–pituitary–adrenal [axis]
HPETE hydroperoxyeicosatetraenoic acid
HRT hormone replacement therapy
HSP heat shock protein
HVA homovanillic acid
IAP inhibitor of apoptosis protein
IC_{50} concentration causing 50% inhibition in the population
ICAM intercellular adhesion molecule
ICE interleukin-1-converting enzyme
ICSH interstitial cell-stimulating hormone
IDDM insulin-dependent diabetes mellitus [now known as type 1 diabetes]
IFN interferon
Ig immunoglobulin
IGF insulin-like growth factor
IL interleukin
Ink inhibitors of kinases
iNOS inducible nitric oxide synthase
INR international normalised ratio
IP inositol phosphate
IP_3 inositol trisphosphate
IP_3R inositol trisphosphate receptor
IP_4 inositol tetraphosphate
ipsp inhibitory postsynaptic potential
IRS insulin receptor substrate
ISI international sensitivity index
ISIS International Study of Infarct Survival
ISO isoprenaline
IUPHAR International Union of Pharmacological Sciences
JRA juvenile rheumatoid arthritis
K_{ACh} potassium channel
K_{ATP} ATP-sensitive potassium [activator, channel]
KIP kinase inhibitory protein
LA local anaesthetic
LC locus coeruleus
LCAT lecithin cholesterol acyltransferase

LD_{50} dose that is lethal in 50% of the population
LDL low-density lipoprotein
LDL-C low-density-lipoprotein cholesterol
LGC ligand-gated cation channel
LH luteinising hormone
LMWH low-molecular-weight heparin
L-NAME N^G-nitro-L-arginine methyl ester
L-NMMA N^G-monomethyl-L-arginine
LQT long QT [channel, syndrome]
LSD lysergic acid diethylamide
LT leukotriene
LTP long-term potentiation
LXR liver oxysterol receptor
lyso-PAF lysoglyceryl-phosphorylcholine
mAb monoclonal antibody
MAC minimal alveolar concentration
mAChR muscarinic acetylcholine receptor
MAGL monoacyl glycerol lipase
MAO monoamine oxidase
MAOI monoamine oxidase inhibitor
MAP mitogen-activated protein
MAPK mitogen-activated protein kinase
MCP monocyte chemoattractant protein
M-CSF macrophage colony-stimulating factor
MDMA methylenedioxymethamphetamine ['ecstasy']
MeNA methylnoradrenaline
methyl-FH_4 methyltetrahydrofolate
MGluR metabotropic glutamate receptor
MHC major histocompatibility complex
MHPEG 3-methoxy-4-hydroxyphenylglycol
MHPG 3-hydroxy-4-methoxyphenylglycol
MIT monoiodotyrosine
MLCK myosin light-chain kinase
MPTP 1-methyl-4-phenyl-1,2,3,5-tetrahydropyridine
MR mineralocorticoid receptor
mRNA messenger ribonucleic acid
MRSA meticillin-resistant *Staphylococcus aureus*
MSH melanocyte-stimulating hormone
NA noradrenaline [norepinephrine]
NAADP nicotinic acid dinucleotide phosphate
NaC voltage-gated sodium channel
nAChR nicotinic acetylcholine receptor
NAD nicotinamide adenine dinucleotide
NADH nicotinamide adenine dinucleotide, reduced
NADPH nicotinamide adenine dinucleotide phosphate, reduced
NANC non-noradrenergic non-cholinergic
NAPBQI *N*-acetyl-*p*-benzoquinone imine
NAPE *N*-acyl-phosphatidylethanolamine
NASA National Aeronautics and Space Administration
NAT *N*-acyl-transferase
NCX Na^+-Ca^{2+} exchange transporter
NET norepinephrine transporter
NF nuclear factor
NFκB nuclear factor kappa B
NGF nerve growth factor
nGRE negative glucocorticoid response element
NIDDM non-insulin-dependent diabetes mellitus [now known as type 2 diabetes]
NIS Na^+/I^- symporter
NK natural killer [cell]
NM normetanephrine
NMDA *N*-methyl-D-aspartic acid
nNOS neuronal nitric oxide synthase [NOS-I]
NNT number needed to treat
NOS nitric oxide synthase
NPR natriuretic peptide receptor
NPY neuropeptide Y
NRM nucleus raphe magnus
NRPG nucleus reticularis paragigantocellularis
NSAID non-steroidal anti-inflammatory drug
ODQ 1H-[1,2,4]-oxadiazole-[4,3-α]-quinoxalin-1-one
OPG osteoprotegerin
oxLDL oxidised low-density lipoprotein
PA partial agonist; phosphatidic acid
PABA *p*-aminobenzoic acid
P_ACO_2 partial pressure of carbon dioxide in arterial blood
PAF platelet-activating factor
PAG periaqueductal grey
PAH *p*-aminohippuric acid
PAI plasminogen activator inhibitor
PAMP pathogen-associated molecular pattern
P_AO_2 partial pressure of oxygen in arterial blood
PAR protease-activated receptor
PARP poly-[ADP-ribose]-polymerase
PC phosphorylcholine
PCPA *p*-chlorophenylalanine

PD Parkinson's disease
PDE phosphodiesterase
PDGF platelet-dependent growth factor
PDS pendrin; paroxysmal depolarising shift
PE phosphatidylethanolamine
PECAM platelet endothelium cell adhesion molecule
PEFR peak expiratory flow rate
PEG polyethylene glycol
PG prostaglandin
PGE prostaglandin E
PGI_2 prostacyclin [prostaglandin I_2]
PI phosphatidylinositol
PIN protein inhibitor of nNOS
PIP_2 phosphatidylinositol bisphosphate
PKA protein kinase A
PKC protein kinase C
PKK cGMP-dependent protein kinase
PL phospholipid
PLA_2 phospholipase A_2
PLC phospholipase C
PLCβ phospholipase Cβ
PLD phospholipase D
Plk Polo-like kinase
PLTP phospholipid transfer protein
PMCA plasma membrane Ca^{2+}-ATPase
PMN polymodal nociceptor
PNMT phenylethanolamine *N*-methyl transferase
PNS peripheral nervous system
Po_2 partial pressure of oxygen
POMC prepro-opiomelanocortin
PPADS pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonate
PPAR peroxisome proliferator-activated receptor
PR progesterone receptor; prolactin receptor
PRF prolactin-releasing factor
PRIF prolactin release-inhibiting factor
Pro-CCK procholecystokinin
pS picosiemens
PT prothrombin time
PTH parathyroid hormone
PTZ pentylenetetrazol
PUFA polyunsaturated fatty acid
PUVA psoralen plus ultraviolet A
QALY quality-adjusted life year
R & D research and development
RA rheumatoid arthritis
RAMP receptor activity-modifying protein
RANK receptor activator of nuclear factor kappa B
RANKL RANK ligand
RANTES regulated on activation normal T-cell expressed and secreted (chemokine)
RAR retinoic acid receptor
Rb retinoblastoma
REM rapid eye movement [sleep]
RGS regulator of G-protein signalling
RIMA reversible inhibitor of the A-isoform of monoamine oxidase
RNA ribonucleic acid
RNAi ribonucleic acid interference
ROS reactive oxygen species
rRNA ribosomal ribonucleic acid
RTI reverse transcriptase inhibitor
RTK receptor tyrosine kinase
RXR retinoid X receptor
RyR ryanodine receptor
SA sinoatrial
SAH subarachnoid haemorrhage
SCF stem cell factor
SCID severe combined immunodeficiency
SERCA sarcoplasmic/endoplasmic reticulum APTase
SERM selective (o)estrogen receptor modulator
SERT serotonin transporter
SG substantia gelatinosa
SH sulfhydryl [e.g. –SH group]
siRNA small [short] interfering ribonucleic acid (see also sRNAi below)
SLE systemic lupus erythematosus
SNAP *S*-nitrosoacetylpenicillamine
SNOG *S*-nitrosoglutathione
SNRI serotonin/noradrenaline reuptake inhibitor
SOC store-operated calcium channel
SOD superoxide dismutase
SP substance P
SR sarcoplasmic reticulum
sRNAi small ribonucleic acid interference (see also siRNA above)
SRS-A slow-reacting substance of anaphylaxis
SSRI selective serotonin reuptake inhibitor
STX saxitoxin