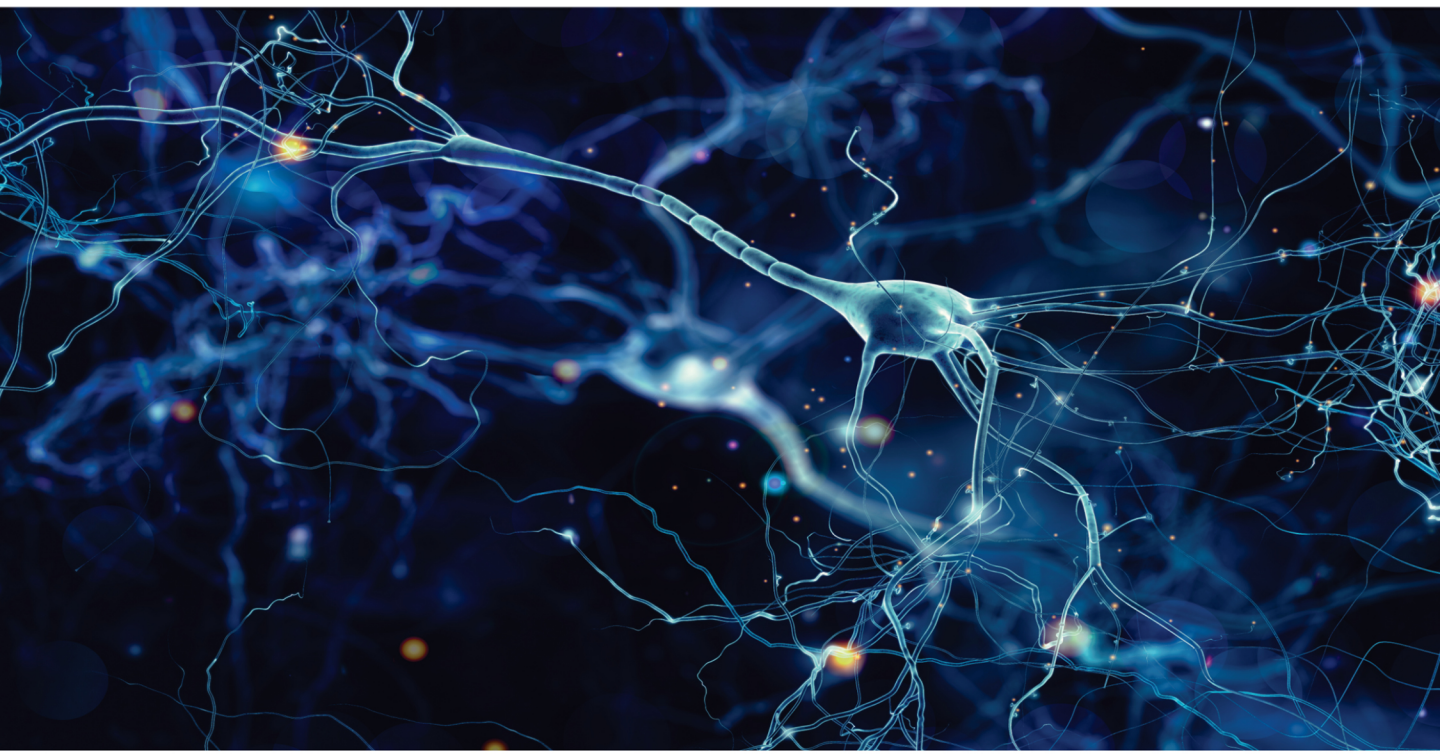
Advances in **Neuropharmacology**

Drugs and Therapeutics



Editors

Md. Sahab Uddin | Mamunur Rashid

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Edited by

Md. Sahab Uddin

Mamunur Rashid

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Dedication

This book is dedicated to
our beloved parents.

About the Editors

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Md. Sahab Uddin, RPh, is a Registered Pharmacist and a Research Scholar in the Department of Pharmacy at Southeast University, Dhaka, Bangladesh. He has published copious articles in peer-reviewed international scientific journals. He has also authored and edited several books, including *Handbook of Research on Critical Examinations of Neurodegenerative Disorders*; *Oxidative Stress and Antioxidant Defense: Biomedical Value in Health and Diseases*; *Comprehensive MCQs in Pharmacology*; *Comprehensive MCQs in Physical Pharmacy*; *Tools of Pharmacy: Getting Familiar with the Regular Terms, Words and Abbreviations*; and *Quality Control of Pharmaceuticals: Compendial Standards and Specifications*. Md. Uddin also serves as a guest editor, editorial and reviewer board member of numerous scholarly journals. He is a member of many national and international scientific societies. He has developed Matching Capacity, Dissimilarity Identification, Numeral Finding, Typo Revealing, and Sense Making tests for the estimation of memory, attention, and cognition. Moreover, he is the Founder and Executive Director of the Pharmakon Neuroscience Research Network, an open innovation hub bringing together neuroscientists to advance brain health. He received his BPharm in 2014 securing a first position from the Department of Pharmacy, Southeast University, Bangladesh. Md. Uddin's research interest is how neuronal operation can be restored to abate Alzheimer's dementia.

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Abbreviations

2-PAM	2-pyridine aldoxime methyl chloride/pralidoxime
3-OMD	3-O-methyldopa
4-DAMP	1,1-dimethyl-4-diphenylacetoxypiperidinium iodide
5-HT	5-hydroxytryptamine/serotonin
8-OHdG	8-hydroxy-2-deoxyguanosine
8-OH-DPAT	8-hydroxy-2-(dipropylamino) tetralin
AAAD	aromatic L-amino acid decarboxylase
AAGBI	Anesthetists of Great Britain and Ireland
ABCC2	ATP-binding cassette sub-family C member 2
ABCC3	ATP-binding cassette sub-family C member 3
AC	adenylyl cyclase
ACE	angiotensin converting enzyme
ACET	kainate receptor antagonist
ACh	acetylcholine
AChE	acetylcholinesterase
ACLS	advance cardiovascular life support
ACNU	nimustine
ACP	anticholinergic drug used in Parkinson's disease
ACTH	adrenocorticotropic hormone
AD	Alzheimer's disease
ADH	alcohol dehydrogenase
ADR	adverse drug reaction
ADT	antidepressant treatment
AEDs	antiepileptic drugs
AGP	α1-acid glycoprotein
AJ	adhesion junction
ALDH	aldehyde dehydrogenase
ALS	amyotrophic lateral sclerosis
AMP	adenosine monophosphate/ adenosine 3',5'-monophosphate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPH	amphetamines
ANS	autonomic nervous system
Anti-ChE	anticholinesterase
APIs	active pharmaceutical ingredients
APP	amyloid precursor protein
ASD	autism spectrum disorder
ASOs	antisense oligonucleotides
ATA	atmospheres absolute
AUC	area under the curve
AUD	alcohol use disorder
AV	atrioventricular
Aβ	amyloid beta
BAC	blood alcohol concentration
BAT	brown adipose tissue
BBB	blood–brain barrier
BChE	butyrylcholinesterase
Bcl-2	B-cell lymphocyte protein-2
BD	bipolar disorder
BDNF	brain-derived neurotrophic factor
BDs	brain disorders
BMEC	brain microvascular endothelial cells
BM-MSC	bone marrow-derived mesenchymal stem cells
BPH	benign prostatic hyperplasia
BuChE	butyrylcholinesterase
BZs/BZDs	benzodiazepines

C6G	codeine-6-glucuronide
CA	catecholamines
CACT	carnitine-acylcarnitine transferase
CAG	cysteine adenosine-guanine
cAMP	cyclic adenosine monophosphate/adenosine-3′,5′-cyclic monophosphate
CAMs	cell adhesion molecules
CAT/ChAT	choline acetyltransferase
CB	cannabinoid receptors
CB1	cannabinoid type 1 receptors
CB1Rs	CB1 receptors
CBZ	carbamazepine
CCK	cholecystokinin
CD	carbidopa
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopy Index Severities Score
CE	cognitive enhancers
cGMP	cyclic guanosine monophosphate/cyclic guanosine 3′,5′-monophosphate
ChAT	choline acetyltransferase
CHD	coronary heart disease
CHF	congestive heart failure
CHO	Chinese hamster ovary
CLD	Creutzfeldt-Jakob disease
C_{max}	maximum plasma concentration
CNF	central neurotrophic factor
CO	carbon monoxide/cardiac output
COMT	catechol-O-methyl transferase
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CP	cerebral palsy
CREB	cAMP response element binding protein
CRF	corticotrophin releasing factor
CSD	cortical spreading depression
CSF	cerebrospinal fluid
CT	computed tomography
CTZ	chemotactic trigger zone
CVS	cardiovascular system
CYP	cytochrome/cytochrome P450
DA	dopamine
DAG	diacylglycerol/1,2-diacylglycerol
DAM	diacetylmonoxime
dbcAMP	adenosine monophosphate
DC	dendritic cell
DCTN1	p150 subunit of dynactin
DFP	di-isopropyl flurophosphonate
DHA	docosahexaenoic acid
DHB	dihydrobunolol
DMPP	dimethylphenylpiperazinium
DNMTs	DNA methyltransferases
DOMA	3,4-dihydroxymandelic acid
DOP/DOR	delta opioid peptide receptor
DOPA	di-hydroxy phenylalanine
DOPAC	3,4-dihydroxyphenylacetic acid
DOPE	dioleoyl phosphatidylethanolamine
DSPC	distearoyl phosphatidylcholine
DSPE	1,2-distearoyl-sn-glycero-3-phosphoethanolamine
DT	diagnostic testing
DUI	driving under the influence
EBC	eye blink conditioning
eCBs	endocannabinoids
ECF	extracellular fluid
ECV	electroconvulsive
EDRF	endothelial derived relaxing factor
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
EKC	[^{3}H]-ethylketocyclazocine
EMG	electromyography
eNOS	endothelial nitric oxide synthase

ENT	extraneuronal amine transporter
EPA	eicosapentaenoic acid
EPN	epinephrine
EPP	excitatory postsynaptic potential
EPS	extrapyramidal symptoms
EPSP	excitatory postsynaptic potential
ERK	extracellular-signal-regulated kinase
ESC	embryonic stem cell
ETC	electron transport chain
FAS	fetal alcohol syndrome
FFI	fatal familial insomnia
FRs	free radicals
FVC	forced vital capacity
GA	glatiramer acetate
GABA	γ-aminobutyric acid
GAD	generalized anxiety disorder/ glutamic acid decarboxylase
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GAT-1	sodium- and chloride-depended GABA transporter 1
GBM	glioblastoma multiforme
GDH	glutamate dehydrogenase
GDP	guanosine diphosphate
GH_3	growth-hormone-secreting pituitary
GHB	γ-hydroxybutyrate
GIRK	G protein-coupled inwardly rectifying K^+ channels
GIT	gastrointestinal tract
GMFM	gross motor function measure
GPCRs	G protein-coupled receptors
GPx	glutathione peroxidase
GSK-3b	glycogen synthase kinase-3beta
GSS	Gerstmann-Straussler-Scheinker syndrome
GTP	guanosine triphosphate
HATs	histone acetylases
HATs	histone acetyltransferases
HBOT	hyperbaric oxygen therapy
HD	Huntington's disease
HDACs	histone deacetylases
HDL	high density lipoprotein
HDLC	high density lipoprotein cholesterol
HEK	human embryonic kidney
HET	human isolated erectile tissue
HIF-1α	hypoxia-inducible factor 1-*α*
HMG-CoA	hydroxymethylglutaryl coenzyme A
HO	heme oxygenase
HPNS	high pressure nervous syndrome
Hpsc	human pluripotent stem cells
HR	heart rate
HTN	hypertension
HVA	homovanillic acid
IBDQ	inflammatory bowel disease questionnaire
IDA-SLN	idarubicin-loaded solid lipid nanoparticles
IM	intramuscular
iNOS	inducible nitric oxide synthase
IOP	intraocular pressure
IP	inositol monophosphate
IP_3	inositol triphosphate/inositol 1,4,5-triphosphate
IPSP	inhibitory postsynaptic potential
iRISA	impaired response inhibition and salience attribution
ISA	intrinsic sympathomimetic activity
IUPHAR	International Union of Basic and Clinical Pharmacology
IVRA	intravenous regional anesthesia
JAM	junction adhesion molecules
KOR	kappa opioid peptide receptor
L-arg	L-arginine

LAs	local anesthetics
LC	locus coeruleus
LCM	lacosamide
LD	levodopa
LDL	low density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDR	long duration response
LEV	levetiracetam
$LOO^{\bullet}$	lipid peroxyl radical
LSD	lysergic acid diethylamide
M	muscarinic
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MAC	minimum alveolar concentration
mAChR	muscarinic acetylcholine receptors
MAG	myelin associated glycoprotein
MAGUK	membrane associated guanylatekinase
MAO	monoamine oxidase
MAO-B	monoamine oxidase B
MAOIs	monoamine oxidase inhibitors
MAPK	mitogen-activated protein kinase
MARCKS	myristoylated alanine-rich PKC-kinase substrate
MCAO	middle cerebral artery occlusion
MCI	mild cognitive impairment
MDCK	madindarby canine kidney
MDRI	multidrug resistance gene
MDZ	midazolam
MEF2	myocyte enhancing factor-2
MEOs	microsomal ethanol-oxidizing system
MI	myocardial infarction
MIT	Massachusetts Institute of Technology
MLAC	minimum local analgesia concentration
MMP9	matrix metalloproteinase 9
MMSE	mini-mental state examination
MMTV	mouse mammary tumor virus
MOP/MOR	μ-opioid peptide receptor
MPH	methylphenidate
MPP^{+}	N-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
MRT	mean residence time
MSA	membrane stabilizing activity
MSN	medium spiny neuron
N	nicotinic
NA	non-adrenergic/noradrenaline
NAc	nucleus accumbens
nAChR	nicotinic acetylcholine receptors
NAD	nicotinamide adenine dinucleotide
NASSAs	noradrenergic specific serotonergic agents
NBOT/NBO	normobaric oxygen therapy
NBQX	AMPA receptor antagonist
NC	non-cholinergic
ncRNAs	non-coding RNAs
NDRIs	noradrenaline and dopamine reuptake inhibitors
NDs	neurodegenerative disorders
NE	norepinephrine
NET	norepinephrine transporter
NF	nanofibers
NFTs	neurofibrillary tangles
NF-κB	nuclear factor-κB
NGF	nerve growth factor
NHERF	Na^{+}/H^{+} exchanger regulatory factor
NIV	non-invasive ventilation
NL	nanoliposomes
NLCs	nanostructured lipid carriers
NMBDs	neuromuscular blocking drugs
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor

NMJ	neuromuscular junction
NMs	nanomaterials
NMS	neuroleptic malignant syndrome
nNOS	neuronal nitric oxide synthase
NOP	nociception/orphanin FQ peptide
NOS	nitric oxide synthase
NPs	nanoparticles
NRM	nucleus raphe magnus
NRPG	nucleus reticularis paragigantocellularis
NSC	neuronal stem cell
NT	neuronal tissue
NTs	neurotrophins
OAB	overactive bladder syndrome
OCD	obsessive-compulsive disorder
OEC	olfactory ensheathing cells
Omgp	oligodendrocyte-myelin glycoprotein
ONH	optic nerve head
$ONOO^-$	peroxynitrite
OXC	oxcarbazepine
p53	tumor supressor protein 53
PABA	para-amino-benzoic acid
$paCO_2$	carbon dioxide tension
PAG	periaqueductal gray
PAM	pralidoxime
PAMPA	parallel artificial membrane permeability assay
PANSS	Positive and Negative Syndrome Scale
PARIs	serotonin partial agonist reuptake inhibitors
PBCA	poly(butyl cyanoacrylate)
PCL	polycaprolactone
PD	panic disorder
PD	Parkinson's disease
PDE	phosphodiesterase
PDI	protein-disulphide isomerase
PDL	poly-D-lysine
PEG	percutaneous endoscopic gastrostomy/polyethylene glycol
PET	positron emission tomography
PGB	Pregabalin
PGE	prostaglandin E
P-gp	P-glycoprotein
PGs	prostaglandins
PHT	phenytoin/fosphenytoin
PIP	phosphatidylinositol monophosphate
PIP_2	phosphatidylinositol 4,5-bisphosphate
PKA	protein kinase A
PKC	protein kinase C
PKG	cGMP dependent protein kinase
PLC	phospholipase C
PLGA	poly(DL-lactic-co-glycolic acid)
PM	pore module
PNS	peripheral nervous system
PO	per oral
pO_2	partial pressure of oxygen
PPARγ	peroxisome proliferator-activated receptor gamma
PR	peripheral resistance
PrD	prion disease
PRL	plasma prolactin
PRO	propofol
PrP	prion protein
PrPSc	prion protease-resistant isoform
PS	permeability surface area product
PS	presenilin
PT	predictive testing
PTB	phenobarbital
PTMA	phenyl trimethyl ammonium
PTSD	post-traumatic stress disorder
QAR	qualitative autoradiography
QD	quantum dot

REM	rapid-eye movement
RNS	reactive nitrogen species
ROCs	receptor-operated channels
ROS	reactive oxygen species
rTMS	repetitive transcranial magnetic stimulation
RXR	retinoid X receptor
SA	sinoatrial
SAD	social anxiety disorder
SAH	aneurysmal subarachnoid hemorrhage
SAR	structure activity relationship
SARIs	serotonin antagonist and reuptake inhibitors
SC	subcutaneous
SDR	short duration response
SF-36	36-Item Short Form Survey
sGC	soluble guanylate cyclase
SMS	serotonin modulator and stimulator
S-NO	S-nitrosylation
SNP	single nucleotide polymorphism
SNpc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SOCs	store operated channels
SOD1	superoxide dismutase-1
SPECT	single-photon emission computed tomography
SSJ	Stevens-Johnson syndrome
SSRIs	selective serotonin reuptake inhibitors
STN	subthalamic nucleus
SV2A	synaptic vesicle glycoprotein 2A
$t_{½}$	half-life
TBZ	tetrabenazine
TC	total cholesterol
TCAs	tricyclic antidepressants
TCTP	translationally controlled tumor protein
TEA	tetramethylammonium
TEER	transendothelial electrical resistance
TEM	transmission electron microscopy
TENS	transcutaneous electrical nerve stimulation
TEPA	tetraethylenepentamine
TG	triglyceride
THC	delta-9-tetrahydrocannabinol
THP	thiopental
TJ	tight junction
TM	thrombomodulin
TMA	tetramethylammonium
TNF-α	tumor necrosis factor-α
TNS	transient neurological symptoms
TPM	topiramate
TRH	thyroid releasing hormone
TrkB	tropomyosin receptor kinase B
TTX	tetrodotoxin
TZDs	thiazolidinediones
UDP	glucuronosyltransferase-2B7
UGT	UDP-glucuronosyltransferase
UGT	uridine diphosphoglucuronosyl transferase
UHDRS	Unified *Huntington's Disease* Rating Scale
UI	urinary incontinence
VAPB/ALS8	vesicle associated membrane protein
V_d	volume of distribution
VEGF	vascular endothelial growth factor
VEP	visual evoked potentials
VGSCs	voltage-gated sodium channels
VMAT	vesicular monoamine transporter
VNS	vagal nerve stimulation
VNT	vesicular neurotransmitter transporter
VOCs	voltage-operated channels
VPA	valproic acid

VSDs	voltage sensor domains	WAT	white adipose tissue
VSSCs	voltage-sensitive sodium channels	Wnt	wingless-type MMTV integration site family
VTA	ventral tegmental area	ZO	zonula occludens

Preface

The nervous system is a complex network of specialized cells known as neurons; understanding of the nervous system and how neurons communicate with one another have become one of the most auspicious areas of research to comprehend the neurological disorders. Neuropharmacology is a very rife region of science that involves countless traits of the nervous system from single neuron manipulation to entire parts of the brain, spinal cord, and peripheral nerves. The prime research of neuropharmacology is to analyze the functions of the brain, spinal cord, sensory systems, and peripheral nerves with the intention to reveal mechanisms of neurological disorders and new approaches for the treatment.

Advances in Neuropharmacology: Drugs and Therapeutics emphasizes the drugs that act on the central and peripheral nervous systems. This book, divided into three parts that consist of 24 chapters, describes the nervous system associated diseases and their treatment as well as current status and future opportunities and challenges. Part I represents the drugs that affect the functions of the autonomic nervous system to produce the therapeutic effects. This section comprises four chapters. Most of the drugs affecting the central nervous system to produce the therapeutic effects primarily act on the steps of neurotransmission. These drugs may act presynaptically by manipulating the genesis, storage, secretion, or blocking the action of neurotransmitters. Some drugs may trigger or impede postsynaptic receptors. Part II focuses on the drugs that affect the central nervous system and comprises 17 chapters. Part III offers neurochemical interactions, aiming at developing drugs that have beneficial effects on neurochemical imbalances, models to assess the transport of drugs across the blood–brain barrier, and nanomedicine to treat brain disorders. This section comprises three chapters.

This book represents the copious set of specific research updates. All over the world numerous erudite, experienced, and eminent academicians, researchers, and scientists participated to write the text of this book to give a precise and diaphanous understanding of drugs affecting the nervous system at a more advanced level with excellent presentation.

This book is suitable for professionals, academicians, students, researchers, scientists, and industrialists around the world. Biomedical, health, and life science departments can use this book as a crucial textbook. Researchers and scientists from research institutes can use the efficient research information presented here. Pharmacists, physicians, and other healthcare professionals can use this book as a reference book. Furthermore, for interested readers, this book is a storehouse of knowledge to help comprehend the complexity of the nervous system acting drugs.

It is expected that readers shall find this book very informative and enormously useful. Since science is constantly changing; readers

are strongly recommended to check for recent updates. The editors are ebulliently ready to accept any comment, suggestion, advice, or critique.

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PART I

Drugs Affecting the Autonomic Nervous System

CHAPTER 1

Cholinergic Agonists

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ABSTRACT

Cholinergic agonists include a wide range of drugs with varied chemical structures and properties. In clinical practice, they are used for the treatment of various diseases, such as glaucoma, myasthenia gravis, belladonna poisoning, paralytic ileus, urinary retention, and reversal of neuromuscular blockade. They also have clinical implication in the treatment of Alzheimer's disease. Use of irreversible anticholinesterase is limited as pesticides or insecticides as they may cause poisoning in humans causing death of a person. This chapter deals with the drugs mimicking cholinergic actions in the periphery at muscarinic receptors. Muscarinic agonists, as a group, or cholinomimetics imitate or mimic the actions of acetylcholine, and hence, such drugs are also called parasympathomimetics. Mainly, they produce effects resembling those of parasympathetic stimulation.

1.1 INTRODUCTION

Drugs acting on the autonomic nervous system (ANS) are classified into two types according to the involvement of type of neuron as cholinergic drugs acting on receptors activated by acetylcholine (ACh) and adrenergic drugs acting on receptors stimulated by noradrenaline or adrenaline (Rang et al., 2011). In the middle of the 19th century, the peripheral nervous system, and particularly the ANS, received a great deal of attention. In 1869, it had been shown that muscarine, an exogenous substance, mimics the effects of stimulating the vagus nerve. Actions of muscarine and vagus nerve stimulation could be inhibited by atropine. It was not until 1921, in Germany, that Loewi showed that excitation of the vagosympathetic trunk connected to an isolated and cannulated frog's heart could cause the release into the cannula of a substance (Vagusstoff) that if the cannula fluid was transported from the first heart to a second, it would inhibit the second heart (Rang et al., 2011).

Studies of Loewi first time provided a direct indication in the involvement of release of chemical substances in nerve impulses (Brunton, 2011). He used two isolated frog hearts. He stimulated vagus nerve of first frog heart. The perfusate of the first frog heart was passed to the second frog heart. Second heart of frog was used as an assessment object. The

second heart of frog responded in the same way as the first heart after a short lag. This proved that a constituent released from the first heart was responsible to slow second heart's rate. He labeled this constituent as Vagusstoff, also known as parasympathin, a vagus substance (Brunton, 2011). Evidence to identify this substance as ACh was provided by Loewi and Navratil. Loewi also proved that when actions of inhibitory fibers are suppressed than the sympathetic fibers in the frog's vagus nerve, Acceleranstoff, an accelerator substance similar to adrenaline, was liberated into the perfusion fluid. According to studies of Feldberg and Krayer in 1933, the cardiac vagus substance is also ACh in mammals (Brunton, 2011). Loewi's findings can be briefed as to the following:

- Perfusate of first frog heart with stimulated vagus caused the appearance of a substance in the perfusate capable of producing an inhibitory effect resembling vagus stimulation in a second heart.
- Sympathetic nervous system stimulation caused the appearance of a substance capable of accelerating a second heart. By fluorescence measurements, Loewi concluded later that this substance was epinephrine.
- Inhibitory action of the vagus on the heart was prevented by atropine but it did not prevent the release of the transmitter, Vagusstoff.
- When Vagusstoff was incubated with ground-up heart muscle, it became inactivated (Rang et al., 2011) due to the enzymatic destruction of ACh by cholinesterase (ChE).

Physostigmine (eserine) prevented the destruction of Vagusstoff by the heart muscle. Vagus stimulation of heart was also stimulated by physostigmine. This evidenced that the stimulation is associated with the inhibition of enzyme ChE involved in the destruction of the transmitter substance ACh (Rang et al., 2011). Synthesis of ACh from choline occurs in the axon terminal of a cholinergic neuron. Transporter helps in uptake of choline into nerve terminal. In nerve terminal, acetylation of free choline occurs in the presence of choline acetyltransferase (CAT). Transfer of acetyl group from acetyl coenzyme A (CoA) occurs in the presence of CAT (Fig. 1.1).

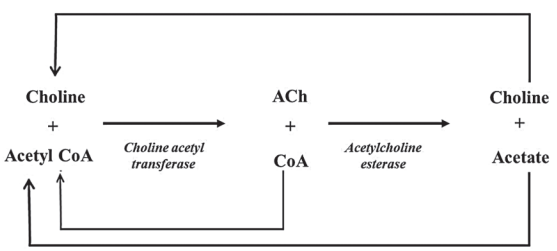

FIGURE 1.1 Synthesis of acetylcholine in cholinergic neuron.

ChE is located in the nerve terminal. ACh is continually hydrolyzed and resynthesized. ACh is stored in the synaptic vesicles. After fusion of the synaptic membrane with axonal membrane, ACh gets released from synaptic vesicles by the process of exocytosis involving Ca^{2+} influx into the nerve terminal. After release, ACh binds with receptors on pre- or postsynaptic membrane (Rang et al., 2011). This chapter deals with the drugs, which act as cholinomimetics in the periphery at muscarinic receptors (mAChRs). Muscarinic agonists, as a group, or cholinomimetics imitate or mimic the actions of ACh. The main effects they produce resemble those of parasympathetic stimulation; hence, such drugs are also called parasympathomimetics.

1.2 CHOLINERGIC RECEPTORS

Muscarinic and nicotinic are mainly two subtypes of cholinergic receptors (Fig. 1.2). The effects of parasympathetic nerve discharge are mimicked by the alkaloid muscarine. Parasympathomimetic effects are effects of muscarine at autonomic neuroeffector junctions and are facilitated by mAChRs (Katzung et al., 2009). Autonomic ganglia and skeletal muscle neuromuscular junctions (NMJs) are stimulated by low concentrations of the alkaloid nicotine due to stimulation of nicotinic receptors (nAChRs). But nicotine does not stimulate autonomic effector cells (Katzung et al., 2009).

1.2.1 MUSCARINIC RECEPTORS AND SIGNAL TRANSDUCTION

ACh is the neurotransmitter of the parasympathetic ANS. Effects of mAChRs are potentiated by ACh (Broadley, 1996). mAChRs are located pre- and postsynaptically. They control transmitter release and are responsible for ganglionic excitation. Effects of ACh at postganglionic synapses located in heart, smooth muscles, and glands are mediated by mAChRs. They are also present in many parts of the central nervous system (CNS) (Rang et al., 2011).

Study of the responses of cells and organ systems in the CNS and periphery helps in the initial differentiation of mAChRs. mAChRs were categorized into two types: M_1 (also called ganglionic) and M_2 (also called effector cell) based on actions of muscarinic agonists, namely, bethanechol and McN-A-343 on the tone of the lower esophageal sphincter (Goyal and Rattan, 1978). mAChRs were identified as M_1–M_5 based on the cloning of the cDNAs encoding five distinct genes for mAChRs (Bonner et al., 1987).

mAChRs belong to G-protein-coupled receptor (Brunton, 2011). Cellular effectors responsible for pharmacological actions produced by activation of mAChRs include formation of second messengers like inositol triphosphate (IP_3) and 1,2-diacylglycerol (DAG) by activation of phospholipase C (PLC), stimulation of potassium (K^+) channels,

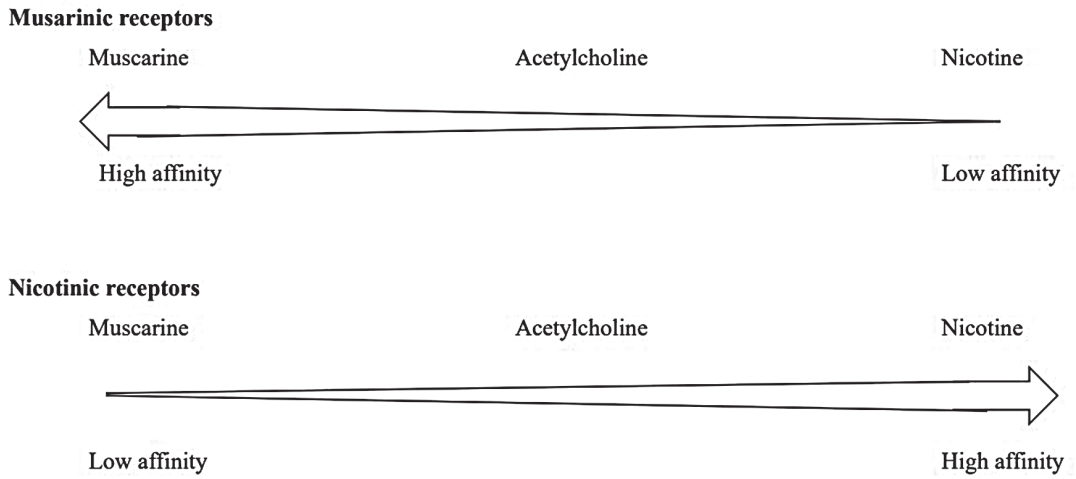

FIGURE 1.2 Categories of cholinergic receptors and its affinity.
Source: Adapted from Harvey et al. (2011).

or inhibition of calcium (Ca^{2+}) channels and adenylyl cyclase (Rang et al., 2011).

1.2.2 M_1 RECEPTORS

M_1 receptors (location: CNS, parietal cells, and neurons in the periphery) facilitate stimulatory effect. Slow muscarinic stimulation in sympathetic ganglia and central neurons by ACh is due to membrane depolarization caused by a decrease in K^+ conductance. A deficit of such type of effects mediated by ACh in the brain may be responsible for dementia (Wess, 2004). Stimulation of M_1 receptors may increase gastric acid secretion following vagal stimulation. Most agonists are nonselective and antagonists show more selectivity, but most of the classic antagonists (e.g., atropine, scopolamine) are nonselective (Rang et al., 2011).

1.2.3 M_2 RECEPTORS

Inhibitory effects of M_2 receptors (location: heart, presynaptic terminals of peripheral and central neurons) are due to an increase in K^+ conductance and inhibition of Ca^{2+} channels. Negative inotropic and chronotropic effects are observed due to stimulation of M_2 receptors causing cholinergic inhibition of heart. Activation of M_2 receptors also shows presynaptic inhibition in the CNS and periphery. Visceral smooth muscles reveal involvement of M_2 and M_3 in the stimulation of smooth muscles in various organs by muscarinic agonists (Rang et al., 2011).

1.2.4 M_3, M_4, AND M_5 RECEPTORS

Excitatory effects such as stimulation of glandular secretions (bronchial, sweat, salivary, etc.) and visceral smooth muscle contraction are produced by M_3 receptors. Release of nitric oxide by adjacent endothelial cells is the key factor in relation to smooth muscle (mainly vascular) enriched with the M_3 receptors (Wess, 2004).

M_4 and M_5 are molecular mAChR mainly restricted to the CNS (Rang et al., 2011). Their functional role is not much clear, but their absence shows behavioral changes in mice (Wess, 2004).

The pharmacological response of mAChRs is mediated through the third intracellular loop of G protein. Receptor stimulation by agonist facilitates guanosine diphosphate (GDP)–guanosine triphosphate (GTP) exchange. This exchange helps in binding of γ-subunit present in G protein. Cleaving of γ-subunit occurs from α-subunit and β-subunit. Stimulation or inhibition of the activity of intracellular enzymes involved in the production of second messengers linked to the tissue response is due to GTP-bound γ-subunit. Activation of M_1, M_3, and M_5 occurs by the involvement of Gq of G-protein-stimulating PLC. Phosphoinositides like phosphatidylinositol 4,5-biphosphate get hydrolyzed by PLC to form IP_3 and DAG. Smooth muscle contraction and glandular secretion affect Ca^{2+} release due to binding of IP_3 to receptors on intracellular sarcoplasmic reticulum store for Ca^{2+}. Protein phosphorylation associated with muscle contraction and influx of Ca^{2+} is due to protein kinase C activated by DAG. M_2 and M_4 receptors involve Gi protein and adenylyl cyclase. Inhibition of adenylyl cyclase decreases levels of cyclic adenosine 3′,5′-monophosphate (cAMP) from ATP after cleavage of GTP-bound γ-subunit of the G protein. Stimulation of cAMP-dependent protein kinase after the formation of cAMP is involved in phosphorylation of many substrates responsible for tissue responses. In the heart,

M_2 receptor may be associated directly with ion channels through G protein without an intermediate second messenger (Caulfield and Birdsall, 1998; Hulme et al., 1990; Caulfield, 1993; Eglen et al., 1996). Properties of mAChRs are given in Table 1.1.

1.2.5 NICOTINIC RECEPTORS AND SIGNAL TRANSDUCTION

nAChRs are of two subtypes depending on their location. Nm subtypes of nAChRs are located in the NMJ. Plasma membranes of postganglionic cells in the autonomic ganglia contain Nn receptors belonging to a ligand-gated ion channel. Subunits of nAChRs form cation-selective channels. They are transmembrane polypeptides (Katzung et al., 2009).

1.3 CLASSIFICATION OF CHOLINERGIC AGONISTS

Based on their actions, cholinergic agonists are classified into three groups as direct acting, indirect acting, and reactivators of acetylcholinesterase (AChE). Classification of cholinergic agonists is given in Table 1.2.

1.4 MECHANISM OF ACTION OF CHOLINOMIMETIC DRUGS

Direct-acting cholinomimetics act by binding to and activating muscarinic and nicotinic receptors. ACh gets hydrolyzed of choline and acetic acid by an enzyme AChE. Indirect acting agents increase the endogenous concentration of ACh in the synaptic cleft and neuroeffector junctions by inhibition of AChE. The excess ACh, in turn, stimulates cholinoceptors to induce increased responses (Brunton, 2011).

Cholinomimetics act mainly at sites where ACh is released to amplify its effects. Some ChE inhibitors also inhibit butyrylcholinesterase (BuChE) (pseudocholinesterase). BuChE is not important in the physiologic termination of indirect-acting cholinomimetic drugs. Hence, its inhibition is less important in the action of indirect-acting cholinomimetic drugs. Some quaternary ChE-inhibitors, for example, neostigmine, show a modest direct action as well by activating neuromuscular nicotinic cholinergic receptors along with blockade of ChE (Brunton, 2011).

1.5 PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE OF DIRECTLY ACTING CHOLINERGIC AGONISTS

1.5.1 PHARMACOKINETICS

As choline esters are hydrophilic in nature, they are absorbed and distributed poorly into the CNS. Susceptibility of all choline esters to hydrolysis by ChE is different and is less active by oral route as they get hydrolyzed in the gastrointestinal (GI) tract (Brunton, 2011).

1.5.1.1 DISTRIBUTION AND FUNCTION

ChEs are of two types: AChE and BuChE with molecular structure resemblance and difference in distribution, specificity for substrate, and functions (Chatonnet and Lockridge, 1989). Normally, AChE and BuChE between them keep the plasma ACh at an undetectably low level, so ACh is strictly a neurotransmitter and not a hormone. The bound AChE at cholinergic

TABLE 1.1 Properties of Muscarinic Receptors.

Receptor subtype	Term	Locations	Subtype of G-protein	Postreceptor mechanisms	Selective agonists	Selective antagonists
M_1	Neural	Nerves	Gq/11 protein-linked	Inositol triphosphate-diacylglycerol cascade	McNA343, oxotremorine	Pirenzepine
M_2	Cardiac	Smooth muscle, heart, nerves	Gi/0 protein-linked	cAMP production inhibition, potassium channel activation	–	Darifenacin, gallamine
M_3	Smooth muscle/ glandular	Glands, endothelium, smooth muscle	Gq/11 protein-linked	Inositol triphosphate-diacylglycerol cascade	Cevimeline	Darifenacin
M_4	–	CNS	Gi/0 protein-linked	cAMP production inhibition	–	Mamba toxin Muscarinic toxin 3 (MT3)
M_5	–	CNS	Gq/11 protein-linked	Inositol triphosphate-diacylglycerol cascade	–	–

cAMP, cyclic adenosine 3′,5′-monophosphate; CNS, central nervous system.

Source: Millar (2003) and Katzung et al. (2009).

TABLE 1.2 Classification of Cholinergic Agonists.

Class	Examples
A. Direct acting	
a. ACh and synthetic choline esters	Acetylcholine, bethanechol, carbachol, methacholine
b. Natural alkaloids	Pilocarpine, muscarine, arecoline, lobeline
c. Miscellaneous	Tremorine, oxotremorine
B. Indirect acting (anticholinesterases)	
a. Reversible anticholinesterases	
I. Carbamic acid derivatives	
i. Natural alkaloid	Physostigmine
ii. Quaternary compounds	Neostigmine, pyridostigmine, edrophonium
II. Acridine derivatives	Tacrine
III. Miscellaneous	Donepezil, rivastigmine, galantamine
b. Irreversible anticholinesterases	
I. Organophosphates	
i. Pesticides	Malathion, parathion
ii. War gases	Sarin, tabun, soman
iii. Miscellaneous	Isofluorophate, ecothiopate
II. Carbamate	Propoxur
C. Acetylcholinesterase reactivation	Pralidoxime

Source: Sharma and Sharma (2017) and Harvey et al. (2011).

synapses hydrolyzes the released transmitter and terminate its action rapidly. Soluble AChE present in cholinergic nerve terminals regulates the free ACh concentration from which it may be secreted. The function of the secreted enzyme is not clear yet (Soreq and Seidman, 2001).

AChE and BuChE both belong to the class of serine hydrolases, which includes many proteases, such as trypsin. Two different regions are available on active site of AChE: an anionic site containing glutamate residue binding with choline moiety of ACh and a catalytic esteratic site. An acetylated enzyme and free choline are formed after the transfer of acetyl group of ACh to serine hydroxyl group. Serine acetyl group gets spontaneously hydrolyzed rapidly. The overall turnover number of AChE is extremely high. A single active site hydrolyzes more than 10,000 molecules of ACh per second (Rang et al., 2011).

Difference between AChE and BuChE has been elaborated in Table 1.3 (Taylor et al., 2009; Massoulie et al., 1993).

1.5.2 PHARMACOLOGICAL ACTIONS

1.5.2.1 CARDIOVASCULAR EFFECTS

1.5.2.1.1 Heart

Directly acting cholinergic agonists show cardiac slowing. Sharp fall in arterial pressure is due to a decreased force of contraction of the atria decreasing cardiac output (CO) and nitric oxide-mediated generalized vasodilatation.

TABLE 1.3 Difference Between Acetylcholinesterase and Butyrylcholinesterase.

Parameter	Acetylcholinesterase/ true-cholinesterase	Butyrylcholinesterase/ pseudocholinesterase
Distribution	Peripheral and central tissues, muscle and nerve, motor and sensory fibers, cholinergic and noncholinergic fibers	Skin, liver, brain, and GI smooth muscle; plasma (in soluble form)
Site of synthesis	Cholinergic neurons, muscle, and hematopoietic cells	Liver
Substrate specificity	Limited—quite specific for ACh and closely related esters such as methacholine	Broader—hydrolyzes synthetic substrate butyrylcholine more rapidly than ACh, as well as other esters, such as procaine, succinylcholine, and propanidid (a short-acting anesthetic agent)
Globular catalytic subunits, which constitute the soluble forms found	Cerebrospinal fluid	Plasma

Ventricles have less parasympathetic innervation and low sensitivity to muscarinic agonists (Brunton, 2011).

Primary effects of ACh on the cardiovascular system include vasodilatation, negative inotropic (decrease in the force of contraction), chronotropic (heart rate), and dromotropic (conduction velocity in the AV node) effects (Rang et al., 2011).

Intravenous injection of small dose of ACh sows transient fall in blood pressure (BP) due to generalized vasodilatation mediated by vascular endothelial NO. This effect is usually accompanied by reflex tachycardia.

Bradycardia or atrioventricular (AV) nodal conduction block are direct effects of ACh on the heart and may be observed after considerably larger doses. Stimulation of mainly M_3 subtype of mAChRs is involved in generalized vasodilatation after exogenous administration of ACh (Khurana et al., 2004; Lamping et al., 2004). M_3 receptors are present on vascular endothelial cells, despite the apparent lack of cholinergic innervation. NO, endothelium-derived relaxing factor, production occurs after binding of agonist with receptors activating Gq–PLC–IP_3 pathway, leading to Ca^{2+}–calmodulin-dependent activation of endothelial NO synthase (Moncada and Higgs, 1995). NO diffuses to adjacent vascular smooth muscle cells causing relaxation (Furchgott, 1999; Ignarro et al., 1999). Due to various pathophysiological conditions, if the endothelium is damaged, ACh acts predominantly on M_3 receptors located on vascular smooth muscle cells, causing vasoconstriction (Brunton, 2011).

1.5.2.1.2 Blood Vessels

Muscarinic agonists act on blood vessels and show generalized vasodilation due to availability of M_3 receptors on the endothelial lining of the vessel. They show fall in BP though they do not have a parasympathetic supply. Stimulation of M_3 receptors releases NO by the action of nitric oxide synthase on L-arginine. NO causes accumulation of cyclic guanosine monophosphate (cGMP) responsible for smooth muscle relaxation (Sneddon and Graham, 1992).

1.5.2.2 EFFECTS ON THE GASTROINTESTINAL TRACT

M_1 receptors are located in the parasympathetic ganglia of the gastric intramural plexus (Kromer and Eltze, 1991). Muscarinic (M_3) agonists increase gut motility, smooth muscle contraction, and secretions of gastric acid from parietal (oxyntic) cells of the stomach and digestive enzymes throughout the gut. Bethanechol, a nonselective agonist, increases intestinal motility and is used in the treatment of postoperative gastric distension and atony and in nonobstructive paralytic ileus (Goyal, 1989). Muscarinic agonists cause colicky pain due to increased peristaltic activity (Rang et al., 2011). Stimulation of vagal input to the GI tract increases tone, amplitude of contractions, and secretory activity of the stomach and intestine. M_3 receptors are mainly responsible for mediating the cholinergic control of GI motility (Matsui et al., 2002).

1.5.2.3 EFFECTS ON THE RESPIRATORY TRACT

Bronchoconstriction may occur due to a varied stimuli-causing reflex increase in parasympathetic actions. ACh causes bronchoconstriction and increases tracheobronchial secretions interfering with breathing (Rang et al., 2011). ACh stimulates chemoreceptors of the carotid and aortic bodies, primarily by M_3 receptors (Fisher et al., 2004).

1.5.2.4 EFFECTS ON THE URINARY TRACT

Detrusor muscle contraction, increased voiding pressure, and ureteral peristalsis are due to parasympathetic sacral innervations. Control of bladder contraction is facilitated by different mAChR subtypes, mainly M_2 receptors. According to studies with selective antagonists and M_3 knockout mice, M_3 receptor is involved in detrusor muscle contraction (Matsui et al., 2000).

1.5.2.5 EFFECTS ON THE GLANDULAR SECRETION

Stimulation of exocrine glands by ACh causes sweating, lacrimation, and salivation (Rang et al., 2011). M_3 are mainly associated with stimulation of lacrimal, nasopharyngeal, salivary, and sweat glands (Caulfield and Birdsall, 1998). M_1 receptor stimulation may also be involved in increased salivary secretion (Gautam et al., 2004).

1.5.2.6 EFFECTS ON THE EYE

The constrictor pupillae muscle runs circumferentially in the iris, whereas ciliary muscle adjusts the curvature of the lens. They both receive parasympathetic supply to the eye. Activation of mAChRs causes contraction of ciliary muscle pulling the ciliary body forward and inward. Tension on the suspensory ligament of the lens gets relaxed; lens bulges more and reduces its focal length, necessary for the eye to accommodate for near vision. The constrictor pupillae adjusts the pupil in response to changes in light intensity and also regulates the intraocular pressure (IOP). Normal IOP (10–15 mmHg above atmospheric) helps to keep the eye slightly distended. Aqueous humor gets secreted slowly and continuously by the cells of the epithelium covering the ciliary body. Aqueous humor is drained into the canal of Schlemm running around the eye close to the outer margin of the iris. One of the commonest preventable cause of blindness associated with

glaucoma is abnormally raised IOP. In acute glaucoma, IOP increases due to obstruction to drainage of aqueous humor after dilation of the pupil. Folding of the iris tissue impedes the drainage angle. Muscarinic agonists activate constrictor pupillae muscle and lower the IOP. Normal individual show little effect. Increased tension in the ciliary muscle produced by these drugs helps in improving drainage by realigning the connective tissue trabeculae through which the canal of Schlemm passes (Rang et al., 2011).

1.5.2.7 EFFECTS ON THE CNS

Brain shows the presence of all mAChRs (M_1–M_5) (Volpicelli and Levey, 2004). They regulate perceptive function, motor control, hunger, nociception, and other processes (Wess et al., 2007). Muscarinic agonists crossing the blood–brain barrier (BBB) and acting on M_1 receptors produce significant central effects like tremor, hypothermia, increased locomotor activity, and improved cognition (Eglen et al., 1999).

1.5.3 CONTRAINDICATIONS

Most contraindications to the use of muscarinic agonists are predictable consequences of mAChR stimulation and include asthma, chronic obstructive pulmonary disease, urinary or GI obstruction, acid-peptic disease, and cardiovascular disease accompanied by bradycardia, hypotension, and hyperthyroidism. Atrial fibrillation may be precipitated by muscarinic agonists in hyperthyroid patients (Brunton, 2011).

1.5.4 ADVERSE EFFECTS

Diaphoresis, diarrhea, abdominal cramps, nausea/vomiting, and other GI side effects and a sensation of tightness in the urinary bladder and presbyopia are observed. In hypotension, the severe reduction in coronary blood flow may be observed, especially if it is already compromised. These contraindications and adverse effects are generally of limited concern with topical administration for ophthalmic use (Brunton, 2011).

1.6 DIRECT-ACTING CHOLINERGIC AGONISTS

1.6.1 ACETYLCHOLINE

1.6.1.1 CHOLINERGIC TRANSMISSION

During the synthesis of ACh, choline enters the neuron via carrier-mediated transport mechanism (Fig. 1.3). Cytosolic enzyme, CAT, present only in the cholinergic neuron is involved in the choline acetylation utilizing acetyl CoA as a source of the acetyl group.

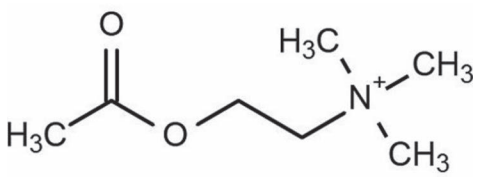

FIGURE 1.3 Chemical structure of acetylcholine.

ACh is packaged into synaptic vesicles at high concentration by carrier-mediated transport (Rang et al., 2011). ACh gets released by exocytosis involving Ca^{2+}. At the NMJ, single presynaptic nerve impulse releases 100–500 vesicles (Fig. 1.4). At "fast" cholinergic synapses, a presynaptic action potential produces only one postsynaptic action potential as ACh is hydrolyzed within about 1 ms by AChE. Transmission mediated by mAChRs is much slower in its time course. ACh functions as a modulator rather

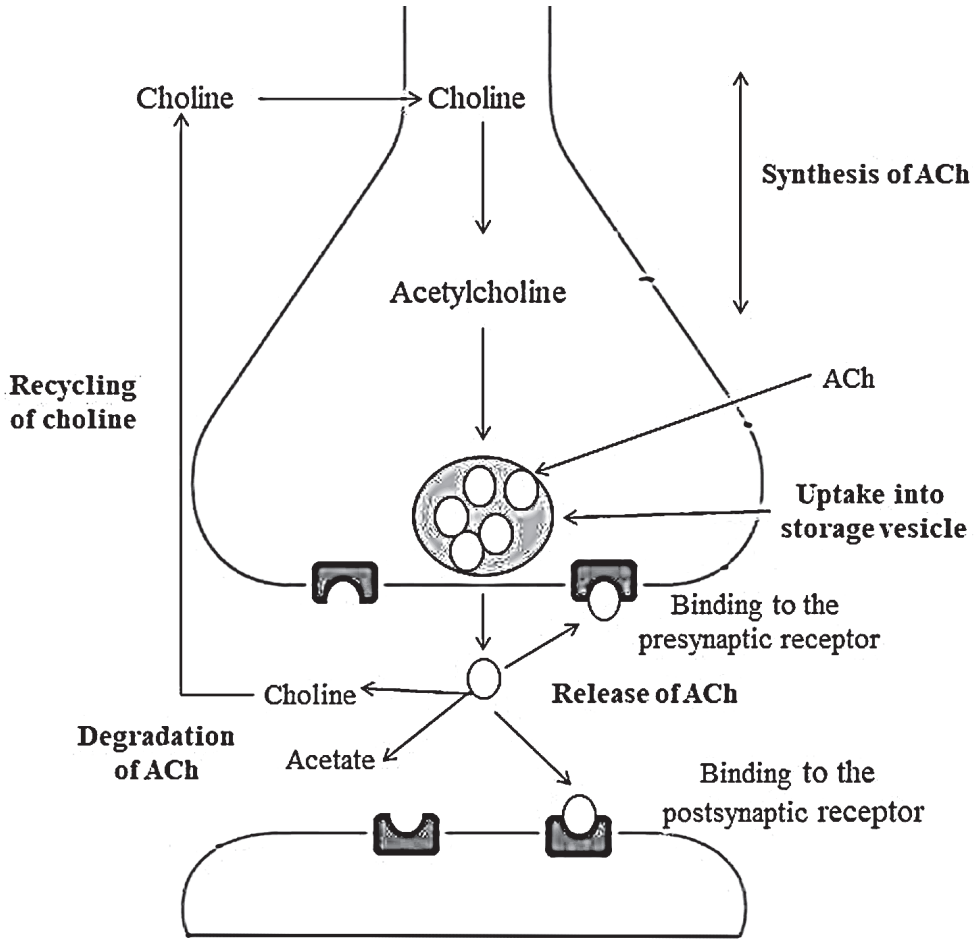

FIGURE 1.4 Mechanism of cholinergic transmission from the cholinergic neuron.
Source: Adapted from Harvey et al. (2011).

than as a direct transmitter in many situations (Rang et al., 2011).

Positively charged quaternary ammonium group and ester group with a partial negative charge are the key features of ACh molecule required for its activity. Ester group is susceptible to rapid hydrolysis by ChE. Modifications of the choline ester structure reduce the susceptibility of the compound to hydrolysis by ChE. It also modifies the relative activity on mAChRs (Katzung et al., 2009).

1.6.1.2 PHARMACOKINETICS

ACh is very rapidly hydrolyzed. To attain necessary concentration for producing measurable actions, huge amounts of ACh must be infused intravenously. A large i.v. bolus injection has a short-term action of 5–20 s, whereas only local effects are produced after intramuscular and subcutaneous injections (Katzung et al., 2009).

1.6.1.3 MECHANISM OF ACTION

ACh and other related choline esters are agonists at muscarinic and nicotinic receptors, but they act more effectively on mAChRs (Katzung et al., 2009).

1.6.1.4 THERAPEUTIC USES

ACh is rarely given systemically. It is used topically and instilled into the eye for the induction of miosis during ophthalmologic surgery as a 1% solution (Brunton, 2011).

1.6.1.5 ADVERSE EFFECTS

mAChR-mediated adverse effects include bronchoconstriction, spasm of accommodation, flushing, abdominal cramps, involuntary urination, sweating, and salivation.

Nicotinic receptor-mediated adverse effects are CNS stimulation, twitching, and paralysis of skeletal muscles (Brunton, 2011).

1.6.1.6 CONTRAINDICATIONS

ACh is contraindicated in bronchial asthma, hyperthyroidism, peptic ulcer, myocardial infarction.

1.6.2 BETHANECHOL

1.6.2.1 PHARMACOKINETICS

It is less susceptible to hydrolysis as it is the fusion of carbachol and methacholine with selectivity for mAChRs. It is rarely used in clinical practice (Rang et al., 2011).

1.6.2.2 MECHANISM OF ACTION

Bethanechol is β-methyl analog of acetyl choline and an unsubstituted carbamoyl ester. It is strongly stereoselective for mAChRs showing almost 1000 times more potency with (*S*)-bethanechol than (*R*)-bethanechol (Katzung et al., 2009).

1.6.2.3 PHARMACOLOGICAL ACTIONS

Bethanechol has mainly muscarinic actions through M_3 receptors. It shows prominent effects on GI motility causing peristalsis and increased motility. It increases resting lower esophageal sphincter pressure. It also stimulates urinary bladder. It has little effect on the heart (Brunton, 2011).

1.6.2.4 THERAPEUTIC USES

Bethanechol is very occasionally used to stimulate GI motility or to assist bladder emptying (Brunton, 2011). Its use is restricted in conditions with the absence of organic obstruction with urinary retention and incomplete bladder emptying as in cases of postoperative urinary retention, diabetic autonomic neuropathy, and certain cases of chronic hypotonic, myogenic, or neurogenic bladder (Wein, 1991); catheterization can thus be avoided. When used chronically, 10–50 mg/day 3–4 times may be given orally. When given 1 h before or 2 h after the meal on an empty stomach, it minimizes nausea and vomiting. Bethanechol formerly was used to treat postoperative abdominal distention, gastric atony, gastroparesis, adynamic ileus, and gastroesophageal reflux (Brunton, 2011).

1.6.3 CARBACHOL (CARBAMYLCHOLINE)

1.6.3.1 PHARMACOKINETICS

Carbachol is almost completely resistant to hydrolysis by ChE. It becomes distributed to areas of low blood flow due to long half-life (Brunton, 2011).

1.6.3.2 MECHANISM OF ACTION

Carbachol is an unsubstituted carbamoyl ester. It retains significant nicotinic activity, particularly on autonomic ganglia (Brunton, 2011).

1.6.3.3 THERAPEUTIC USES

Carbachol is used as experimental tools. It is used topically as a 0.01–3% solution and instilled into eye for the treatment of glaucoma and the induction of miosis during surgery (Brunton, 2011).

1.6.4 METHACHOLINE

1.6.4.1 PHARMACOKINETICS

Increased resistance of methacholine to hydrolysis by ChE is due to the methyl group. It has greater duration and selectivity of action (Brunton, 2011).

1.6.4.2 MECHANISM OF ACTION

Methacholine (acetyl-β-methylcholine), the β-methyl analog of ACh, is a synthetic choline ester. It shows predominant selectivity for muscarinic with only minor nicotinic actions. Muscarinic effect is useful in the cardiovascular system (Brunton, 2011).

1.6.4.3 THERAPEUTIC USES

Methacholine is used as an experimental tool. It is administered by inhalation for the diagnosis of bronchial airway hyperactivity in patients who do not have clinically apparent asthma (Crapo et al., 2000). It is used as a powder that is diluted with 0.9% sodium chloride and administered via a nebulizer (Brunton, 2011).

1.6.4.4 ADVERSE EFFECTS

Methacholine can cause bronchoconstriction and increased tracheobronchial secretions in all individuals (Brunton, 2011).

1.6.4.5 CONTRAINDICATIONS/ PRECAUTIONS

Methacholine is contraindicated in asthma, severe airflow limitation, recent myocardial infarction or stroke, uncontrolled hypertension, or pregnancy. The response to methacholine also may be exaggerated or prolonged in patients taking β-adrenergic receptor antagonists. Emergency resuscitation equipment, oxygen, and medications to treat severe bronchospasm (e.g., β_2-adrenergic receptor agonists for inhalation) should be available during testing (Brunton, 2011).

1.6.5 PILOCARPINE

1.6.5.1 PHARMACOKINETICS

Leaflets of South American shrubs of *Pilocarpus microphyllus* contain pilocarpine as the chief alkaloid. Being tertiary amine, pilocarpine readily gets absorbed from most sites of administration and crosses BBB. It mainly

gets excreted through urine. Decreasing pH of the urine promotes its clearance (Katzung et al., 2009). Although the specific metabolic pathways have not been explained, pilocarpine clearance is decreased in patients with hepatic impairment, in whom doses may need to be reduced (Brunton, 2011).

1.6.5.2 MECHANISM OF ACTION

Pilocarpine has a dominant muscarinic action but is a partial agonist (Brunton, 2011).

1.6.5.3 PHARMACOLOGICAL ACTIONS

It shows some selectivity in stimulating secretion from various exocrine glands, such as sweat, salivary, lacrimal, and bronchial glands, and contracting iris smooth muscle. It has weak effects on GI smooth muscle and the heart (Rang et al., 2011). The sweat glands are sensitive to pilocarpine. After isolation of pilocarpine in 1875, shortly thereafter, Weber described its actions on the pupil and on the sweat and salivary glands (Brunton, 2011).

1.6.5.4 THERAPEUTIC USES

Currently, natural alkaloids like pilocarpine are used clinically as a sialagogue and miotic agent (Brunton, 2011). Pilocarpine can cross the conjunctival membrane. It is a stable compound and its actions last for about 1 day (Rang et al., 2011). Pilocarpine hydrochloride is used in the treatment of xerostomia due to head and neck radiation treatments or associated with Sjogren's syndrome (Porter et al., 2004; Wiseman and Faulds, 1995). Sjogren's syndrome is an autoimmune disorder occurring primarily in women with altered secretions of lacrimal and salivary glands (Anaya and Talal, 1999). If salivary parenchyma maintains residual function, enhanced salivary secretion, ease of swallowing, and subjective improvement in hydration of the oral cavity are achieved. The usual dose is 5–10 mg three times daily; the dose should be lowered in patients with hepatic impairment. Pilocarpine is used topically in ophthalmology for the treatment of glaucoma and as a miotic agent. It is instilled in the eye as a 0.5–6% solution or may be delivered via an ocular insert (Brunton, 2011).

1.6.5.5 ADVERSE EFFECTS

Adverse effects are due to stimulation of cholinergic system. Sweating is the common side effect (Brunton, 2011).

1.6.6 MUSCARINE

Schmiedeberg in 1869 isolated alkaloid muscarine from the mushroom *Amanita muscaria*. Muscarine acts mainly at mAChR sites. The classification of these receptors derives from the actions of this alkaloid. Muscarine, a quaternary amine, is poorly absorbed following oral administration and does not cross the BBB easily. Even though these drugs resist hydrolysis, the choline esters are short-acting agents due to rapid elimination by the kidneys. Muscarine can still, however, be toxic when ingested and can even have CNS effects (Brunton, 2011).

1.6.7 ARECOLINE

It is the main alkaloid obtained from seeds of areca or betel nuts, that is, *Areca catechu*. It acts at nicotinic receptors. Being tertiary amine, it readily gets absorbed and crosses BBB. Natives

of the Indian subcontinent and East Indies were consuming this red staining betel nut as a euphoric, a mixture containing nut, shell lime, and leaves of a climbing species of pepper, *Piper betle* (Brunton, 2011).

1.6.8 POISONING

Exaggeration of various parasympathetic effects was shown after poisoning from the ingestion of plants containing pilocarpine, muscarine, or arecoline, and they resemble those produced after ingestion of genus *Inocybe*. Atropine should be given parenterally in large doses to cross BBB. Supportive measures for respiratory and cardiovascular systems and to counteract pulmonary edema may also be used (Brunton, 2011).

1.7 INDIRECT-ACTING CHOLINERGIC AGONIST (ANTICHOLINESTERASES)

ChE inhibitors affect peripheral and central cholinergic synapses. Most of the peripherally acting anti-ChE drugs inhibit AChE and BuChE about equally (Fig. 1.5). Centrally acting anti-ChEs are developed for the treatment of dementia (Rang et al., 2011).

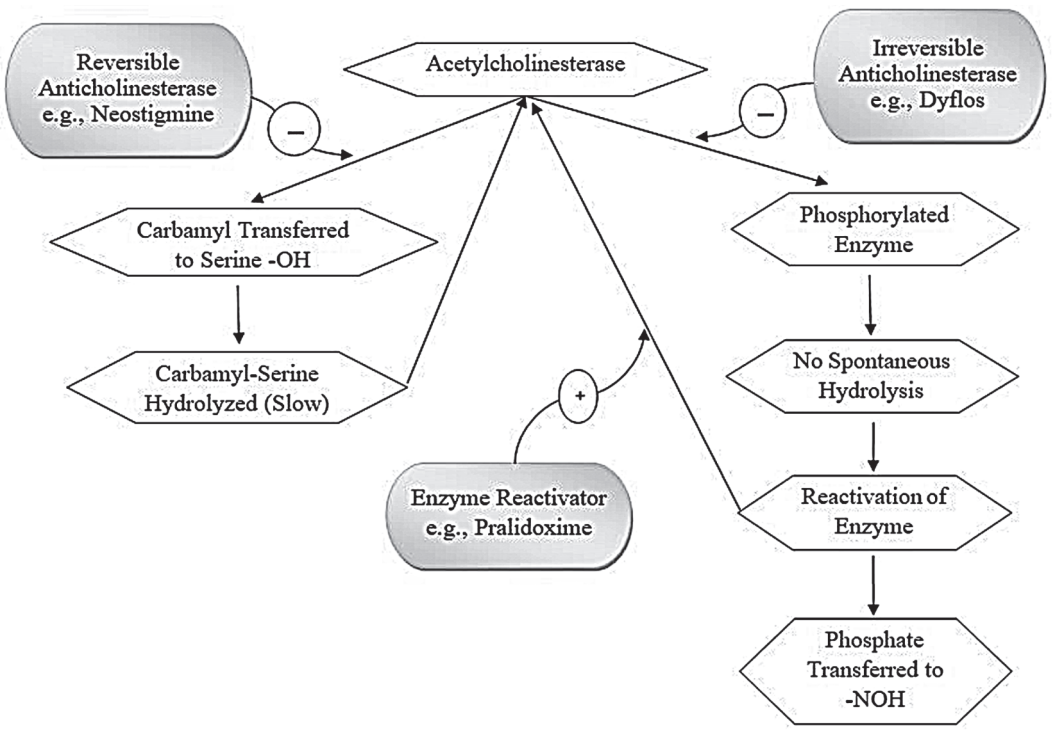

FIGURE 1.5 Mechanism of action of indirect-acting cholinergic agonists. For reversible anti-ChE, for example, neostigmine, the recovery of activity by hydrolysis of the carbamylated enzyme takes many minutes. In case of irreversible anti-ChE, for example, dyflos, the reactivation of phosphorylated enzyme is accomplished by pralidoxime.

Source: Adapted from Rang et al. (2011).

1.7.1 REVERSIBLE ANTICHOLINESTERASES

At physiological pH, physostigmine and neostigmine possess positive charge, by serving as alternate substrates to ACh and generate carbamoylated enzyme by attacking the active center serine. Methylcarbamoyl AChE and dimethylcabamoyl AChE ($t_{1/2}$ for hydrolysis: 15–30 min) are more stable than acetyl enzyme (Sharma and Sharma, 2017).

1.7.1.1 CARBAMIC ACID DERIVATIVES

These are all carbamyl-possessing basic group binding with the anionic site. Like ACh, the transfer of carbamyl group to the serine hydroxyl group of the esteratic site occurs. The carbamylated enzymes get hydrolyzed slowly. It takes minutes for hydrolysis (Brunton et al., 2011). The anti-ChE drug gets hydrolyzed at a negligible rate compared with ACh. They are responsible for the slow recovery of the carbamylated enzyme, increasing the duration of action of these compounds (Brunton et al., 2011).

1.7.1.1.1 Natural Alkaloid

1.7.1.1.1.1 Physostigmine

Physostigmine/eserine, a tertiary amine, is an alkaloid isolated by Jobst and Hesse in 1864. It was obtained from Calabar (ordeal) bean that was obtained from the dried, ripe seeds of a perennial plant of *Physostigma venenosum*. Calabar beans were used in witchcraft trials, in which guilt was judged by death from the poison, innocence by survival after ingestion of a bean. For the first time in 1877, physostigmine was used therapeutically that Laqueur used for the treatment of glaucoma during his clinical practice (Karczmar, 1970; Holmstedt, 2000; Brunton, 2011).

1.7.1.1.1.1.1 Pharmacokinetics

The absorption of physostigmine from the gastrointestinal tract, mucous membrane, and subcutaneous tissues are easy. Systemic effects may be observed after conjunctival instillation of solutions, if absorption from the nasal mucosa is not restricted. Hydrolytic cleavage of parenterally administered physostigmine occurs within 2–3 h by plasma esterases. Elimination by renal route is very less (Brunton, 2011).

1.7.1.1.1.1.2 Mechanism of Action

It is a carbamic acid ester and a substrate for AChE forming a relatively stable carbamoylated intermediate with the enzyme which then becomes reversibly inactivated. This results in the potentiation of cholinergic activity throughout the body (Harvey et al., 2011). Methyl carbamate of an amine-substituted phenol is an essential moiety of the physostigmine (Brunton, 2011).

1.7.1.1.1.1.3 Pharmacological Actions

Physostigmine has a broad variety of actions which is due to the stimulation of muscarinic and nicotinic sites of the ANS and nicotinic receptors of the NMJ. It crosses BBB to stimulate cholinergic receptors in the CNS. Its duration of action is about 2–4 h (Brunton, 2011).

1.7.1.1.1.1.4 Therapeutic Uses

Physostigmine is used in atony of intestine and bladder as it increases their motility. It can be used to treat glaucoma as it produces miosis and spasm of accommodation as well as a lowering of IOP when instilled in the eye. It can be used to treat glaucoma, but pilocarpine is more effective. Also, it is used in the treatment of

overdosage of drugs with anticholinergic drugs, such as atropine, phenothiazine, and tricyclic antidepressants (Brunton, 2011).

1.7.1.1.1.1.5 Adverse Effects

In high doses, physostigmine affects CNS and may lead to convulsions. Bradycardia and fall in CO may also occur. Inhibition of AChE at NMJ leads to its deposition which causes paralysis. These effects are rarely seen in therapeutic doses (Harvey et al., 2011).

1.7.1.1.2 Quaternary Compounds

1.7.1.1.2.1 Neostigmine and Pyridostigmine

1.7.1.1.2.1.1 Pharmacokinetics

Larger doses of neostigmine and pyridostigmine are needed than by the parenteral route as absorption after oral administration is very poor. Both are destroyed by plasma esterases, $t_{1/2}$ is only 1–2 h. The parent compounds, as well as quaternary aromatic alcohols, are excreted via urine. Neostigmine is effective at 0.5–2-mg parenteral dose and the corresponding oral dose range between 15 and 30 mg or more (Cohan et al., 1976; Brunton, 2011).

1.7.1.1.2.1.2 Mechanism of Action

They reversibly inhibit AChE similar to physostigmine. They have quaternary nitrogen. They are more polar and do not cross BBB. Their effect on skeletal muscle is greater than that of physostigmine. Before skeletal muscle gets paralyzed, they stimulate contractility (Brunton, 2011).

1.7.1.1.2.1.3 Therapeutic Uses

Neostigmine stimulates the bladder and GIT. It is used as an antidote for tubocurarine and other competitive neuromuscular blockers and also in the symptomatic treatment of myasthenia gravis (Brunton, 2011). Pyridostigmine has slight (3–6 h) longer duration of action than neostigmine, it does not penetrate BBB and used in the chronic treatment of myasthenia gravis (Brunton, 2011).

1.7.1.1.2.1.4 Adverse Effects

Neostigmine and pyridostigmine show adverse effects like flushing, salivation, nausea, abdominal pain, diarrhea, bronchial spasm, and decreased BP (Harvey et al., 2011).

1.7.1.1.2.2 Edrophonium

1.7.1.1.2.2.1 Pharmacokinetics

It is more rapidly absorbed. The activity of edrophonium is partial to synapses of the parasympathetic nervous system, has a reasonable attraction for AChE, and binds reversibly to the AChE active center. It is short-acting anti-ChE (duration of action: 10–20 min) with a limited volume of distribution and rapid renal elimination. Quaternary structure of edrophonium facilitates renal elimination (Brunton, 2011).

1.7.1.1.2.2.2 Mechanism of Action

It is a synthetic, quaternary ammonium compound forming a readily reversible ionic bond by binding with anionic site of the enzyme (Sharma and Sharma, 2017).

1.7.1.1.2.2.3 Therapeutic Uses

It is used mainly in the diagnosis of myasthenia gravis. Muscle weakness due to causes other than myasthenia gravis is not improved by an anti-ChE. Rapid increase in muscle strength is observed after i.v. injection (2 mg). An excess drug may provoke a cholinergic crisis and atropine may be used as an antidote (Harvey et al., 2011).

1.7.1.2 ACRIDINE DERIVATIVE

1.7.1.2.1 Tacrine

Tacrine is more hydrophobic with a higher affinity for AChE. It inhibits the activity of AChE in the brain as it easily crosses the BBB. Partionining into lipid and higher affinity for AChE are responsible for a longer duration of action (Brunton, 2011).

1.7.1.3 MISCELLANEOUS

1.7.1.3.1 Donepezil

It is a more selective AChE inhibitor used in Alzheimer's patients for the management of cognitive dysfunction associated with it. It is more hydrophobic, longer half-life, and administered once daily. It lacks the hepatotoxic effect of tacrine (Katzung et al., 2009).

1.7.1.4 THERAPEUTIC USES

The clinical uses of anti-ChEs are as follows:

- Neostigmine: At the end of an operation, it reverses the action of nondepolarizing neuromuscular blockers.
- Pyridostigmine or neostigmine: Treatment of myasthenia gravis.
- Edrophonium: A short-acting drug, given intravenously in the management of myasthenia gravis and to differentiate between muscle paralysis due to myasthenia gravis or cholinergic crisis at the motor end plate.
- Donepezil: In Alzheimer's disease.
- Ecothiopate: In glaucoma, as an eye drops (Katzung et al., 2009).

1.7.2 IRREVERSIBLE ANTICHOLINESTERASES

This group includes organophosphate (OP) compounds, such as war gases and pesticides, and carbamates.

1.7.2.1 MECHANISM OF ACTION

These compounds belong to pentavalent phosphorus group having fluoride as a labile group (in dyflos) or an organic group present in parathion and ecothiopate. This group gets released, by separating the serine hydroxyl molecule of the phosphorylated enzyme. Majority of the OP compounds were prepared for used as war gases, pesticides, and for clinical applications. They do not have cationic group except ecothiopate (contains quaternary nitrogen group binding with the anionic site). They interact only with the esteratic site of the enzyme (Katzung et al., 2009). The inactive phosphorylated enzyme is usually very stable. Significant hydrolysis does not occur with drugs such as dyflos and revival of enzyme activity based on the synthesis process of the new enzyme. The mechanism of action of ecothiopate is not firmly irreversible as the hydrolysis of drugs occurs slowly over the period of a few days (Katzung et al., 2009). As dyflos and parathion rapidly get absorbed from mucous membranes, steady skin, and insect cuticles, they are used as war gases or insecticides. They are nonpolar, volatile, and highly lipid soluble substances. They block other serine hydrolases (e.g., trypsin, thrombin) and may lack specificity—conferring to the quaternary group, although their pharmacological effects result mainly from ChE inhibition (Sharma and Sharma, 2017).