

Contents

Section I: Introduction to Neuronal Nicotinic Receptors

CHAPTER 1

The History of the Neuronal Nicotinic Receptors

D.A. BROWN	3
A. The Autonomic Ganglion: The Archetypical Neuronal Nicotinic Receptor	3
B. Nicotinic Acetylcholine Receptors in the Central Nervous System	5
C. Presynaptic Nicotinic Receptors	7
References	8

CHAPTER 2

Distribution of Cholinergic Neurons in the Mammalian Brain with Special Reference to their Relationship with Neuronal Nicotinic Acetylcholine Receptors

M. ZOLI. With 1 Figure	13
A. Distribution of Cholinergic Neurons in Neural Tissues	13
I. The Basal Telencephalic System	13
II. Striatal Interneurons	15
III. The Habenulo-Interpeduncular System	15
IV. The Mesopontine Tegmental System	16
V. Brainstem and Spinal Cord Motor Nuclei	16
VI. Medullary Tegmentum	16
VII. Peripheral Ganglia and Retina	17
VIII. Putative Cholinergic Systems	17
IX. Comparative Aspects	17
B. Distribution of Nicotinic Receptors with Respect to Cholinergic Neurons	20
I. Location of nAChRs in Cholinergic and Cholinoceptive Cells	20
1. Heteroreceptors	21

2. Subunit Composition of Heteroreceptors	22
3. Autoreceptors	23
4. Subunit Composition of Autoreceptors	24
II. Wiring Vs Volume Transmission in Cholinergic Systems	24
References	26

Section II: Genes, Structure, and Distribution of Neuronal Nicotinic Receptors

CHAPTER 3

Gene Structure and Transcriptional Regulation of the Neuronal Nicotinic Acetylcholine Receptors

J.-M. MATTER and M. BALLIVET. With 4 Figures	33
A. Background	33
B. Functional Groupings and Gene Structure	34
I. Function and Sequence Homology Scores	35
II. Function and Gene Structure	36
C. Expression and Regulation of the Neuronal nAChR Genes	39
I. nAChRs in the Adult Retina	39
II. nAChRs in the Developing Retina	40
III. Role of Innervation and Target Tissues on nAChR Expression	41
D. Identification of Cis-acting Regulatory Elements	43
I. nAChR Genes as a Model for Neuron-Specific Gene Transcription	43
II. Technical Tools to Investigate Transcriptional Regulation	43
III. Identification of Cis-acting Elements that Regulate Transcription	44
1. The $\beta 2$ Gene – The Role of Silencing Elements	44
2. The $\alpha 7$ Gene	45
3. $\alpha 3$ and $\beta 4$ – The Role of Ubiquitous Transcription Factors	46
IV. A Network of Neuronal bHLH Transcription Factors Regulates $\beta 3$ in Retina	47
References	49

CHAPTER 4

Transcriptional Regulation of Neuronal nAChR Subunit Genes

E.S. DENERIS. With 3 Figures	57
A. Introduction	57
B. Cell-Type Specific Transcription	59
C. DNA Regulatory Elements and Transcription Factors	60
I. $\alpha 2$ Gene	60
1. Avian $\alpha 2$ Regulatory Region	60
2. $\alpha 2$ Silencer Region	60
II. $\alpha 7$ Gene	61
1. Chicken $\alpha 7$ Promoter	61
2. Bovine $\alpha 7$ Promoter	61
III. $\beta 2$ Gene	63
1. Mouse $\beta 2$ Promoter	63
2. Transgenic Analysis of the $\beta 2$ Promoter	63
3. $\beta 2$ Neuron Restrictive Silencer Element	64
IV. $\beta 4$, $\alpha 3$, $\alpha 5$ Gene Cluster	64
1. Rat $\beta 4$ Promoter	65
2. Rat and Human $\alpha 3$ Promoters	66
3. Activation of the Rat $\alpha 3$ Promoter by the POU Factor, SCIP	68
4. Transgenic Analysis of Rat $\alpha 3$ Upstream Region	69
5. Rat $\beta 43'$ Enhancer	69
D. Conclusions and Future Directions	73
References	73

CHAPTER 5

Contributions of Studies of the Nicotinic Receptor from Muscle to Defining Structural and Functional Properties of Ligand-Gated Ion Channels

P. TAYLOR, H. OSAKA, B. MOLLES, S.H. KELLER, and S. MALANY. With 4 Figures	79
A. Introduction	79
B. Functional Aspects of the Nicotinic Receptor in Skeletal Muscle	81
C. Isolation and Characterization of Nicotinic Receptors	82
D. Structure of the Muscle Nicotinic Receptor	83
E. Biophysical Properties of Muscle Receptors	88
F. Natural Toxins that Block Motor Activity	89
G. Congenital Myasthenia Syndromes from Receptor Mutations	91

H. Biosynthesis and Assembly of the Receptor Subunits	93
I. Regulation of Nicotinic Acetylcholine Receptor Expression	95
References	96

CHAPTER 6

The Structures of Neuronal Nicotinic Receptors

J. LINDSTROM. With 3 Figures	101
A. Muscle AChRs Provide the Model for Neuronal AChRs	101
I. Subunits Which Comprise Muscle AChRs	102
II. Structures of the Muscle AChR Subunits	103
III. Organization of Subunits Around the Central Cation Channel	110
IV. Acetylcholine Binding Sites in the Extracellular Domain	110
V. The Main Immunogenic Region in the Extracellular Domain and Myasthenia Gravis	112
VI. Cation-Specific Channel and Its Gate	123
VII. Large Cytoplasmic Domain	123
VIII. AChR Mutations in Congenital Myasthenic Syndromes	124
B. Neuronal AChRs Which Can Function as Homomers	124
I. Subunits Which Comprise Homomeric Neuronal AChRs	125
II. Structures of the Homomeric Neuronal AChR Subunits	127
III. Organization of Subunits Around the Central Channel	128
IV. Special Properties of Homomeric Neuronal AChRs	131
V. Involvement of Homomeric Neuronal AChRs in Diseases	133
C. Heteromeric Neuronal AChRs	134
I. Structures of the Subunits of Heteromeric Neuronal AChRs	137
II. Organization of Subunits Around the Central Channel	139
III. Special Properties of Heteromeric Neuronal AChRs	140
IV. Involvement of Heteromeric Neuronal AChRs in Diseases	144
D. Conclusions and Current Problems	146
References	147

CHAPTER 7

The Distribution of Neuronal Nicotinic Acetylcholine Receptors

P.B. SARGENT. With 3 Figures	163
A. Introduction	163
B. Nicotinic AChRs in Non-neuronal Cells	164
C. Regional Distribution of AChRs Within the Peripheral Nervous System	164
I. Autonomic Ganglia	164
II. Sensory Ganglia	165
D. Regional Distribution of AChRs Within the Central Nervous System	165
I. Mapping Studies with [³ H]Nicotine and with Ligands for $\alpha 4$ and $\beta 2$	166
II. Mapping Studies with ¹²⁵ I- α -Bgt and with Ligands for $\alpha 7$	173
III. Mapping Studies with Ligands for $\alpha 3$	174
IV. Mapping Studies with Ligands for $\beta 4$	174
V. Mapping Studies with Ligands for $\alpha 2$, $\alpha 5$, $\alpha 6$, and $\beta 3$	174
VI. Species Differences among Mammals	175
VII. AChR Mapping in Chicken Brain	176
E. Distribution of AChRs on the Neuronal Surface	176
I. Peripheral Nervous System (see also Chap. 10, this volume)	176
II. Central Nervous System	180
F. Presynaptic AChRs/Extrasynaptic AChRs	182
G. Regulation of AChR Distribution	182
H. Conclusion	184
References	184

CHAPTER 8

Presynaptic Neuronal Nicotinic Receptors:**Pharmacology, Heterogeneity, and Cellular Mechanisms**

S. KAISER, L. SOLIAKOV, and S. WONNACOTT. With 2 Figures	193
A. Introduction	193
B. Pharmacology and Heterogeneity of Presynaptic Nicotinic Receptors	195
I. Acetylcholine	195
II. Dopamine	196
III. Noradrenaline	197
IV. 5-Hydroxytryptamine	198
V. γ -Aminobutyric Acid	199
VI. Glutamate	199

VII. Adenosine Triphosphate	200
VIII. Summary	200
C. Molecular and Cellular Mechanisms Underlying the Nicotinic Modulation of Transmitter Release	201
I. Na ⁺ Dependence and Tetrodotoxin Sensitivity	201
II. Ca ²⁺ Dependence and Involvement of Voltage Operated Ca ²⁺ Channels	201
III. The Involvement of Second Messengers in the Nicotinic Modulation of Neurotransmission	203
1. Protein Kinase C	203
2. CaM Kinase II	205
3. Tyrosine Kinase Signalling Pathways	205
D. Concluding Remarks	206
References	206

CHAPTER 9

Neuronal Nicotinic Acetylcholine Receptors in Development and Aging

M. ZOLI. With 4 Figures	213
A. Development of Neuronal Nicotinic Acetylcholine Receptors	213
I. Development of Neuronal Nicotinic Acetylcholine Receptors in the Peripheral Nervous System	214
1. Phenomenological Aspects	214
2. Mechanistic Aspects	215
3. Conclusions	216
II. Development of Neuronal Nicotinic Acetylcholine Receptors in the Central Nervous System	217
1. Avian Central Nervous System	218
2. Rodent Central Nervous System	218
3. Human Central Nervous System	223
4. Conclusions	224
III. Role of Neuronal Nicotinic Acetylcholine Receptors in the Development of Nicotinoceptive Cells	224
1. Effects of Nicotine Exposure on the Development of the Central Nervous System	225
2. Mechanistic Aspects of the Morphogenetic Actions of Neuronal Nicotinic Acetylcholine Receptors	227
3. Conclusions	228
B. Neuronal Nicotinic Acetylcholine Receptors During Aging	229
I. Neuronal Nicotinic Acetylcholine Receptors During Normal Aging	229
II. Neuronal Nicotinic Acetylcholine Receptors During Pathological Aging	231

III. Role of Neuronal Nicotinic Receptors in Normal and Pathological Aging	232
1. Neuronal Nicotinic Acetylcholine Receptors and Amyloid	233
2. Neuronal Nicotinic Acetylcholine Receptors and Apolipoprotein E	234
3. Neuronal Nicotinic Acetylcholine Receptors and Cell Loss	234
4. Conclusions	235
C. General Conclusions	236
References	237

CHAPTER 10

Nicotinic Acetylcholine Receptors in Ganglionic Transmission

D.K. BERG, R.D. SHOOP, K.T. CHANG, and J. CUEVAS.

With 4 Figures	247
A. Introduction	247
B. Nicotinic Receptor Composition in Ganglia	248
I. Immunological Identification	248
II. Electrophysiological Features	249
C. Subcellular Locations and Postsynaptic Roles	250
I. Synaptic Currents	250
II. Somatic Spines Versus Postsynaptic Densities	252
III. Functional Significance	254
D. Presynaptic Nicotinic Receptors in Ganglia	257
E. Regulation of Ganglionic Nicotinic Receptors	258
I. Receptor Regulation by Cell-Cell Interactions	258
II. Developmental Regulation	259
III. Molecular Controls	260
F. Future Challenges	262
G. References	262

Section III: Functional Properties

CHAPTER 11

**Neuronal Nicotinic Acetylcholine Receptors:
From Biophysical Properties to Human Diseases**

B. BUISSON, F. PICARD, and D. BERTRAND. With 7 Figures	271
A. Introduction	271
B. Reconstitution and Recording of Neuronal nAChRs	274
C. The Allosteric Model	275

D. Functional Domains of the Neuronal nAChR	277
E. The Agonist Binding Site: Structure and Modulations	278
I. Structural Determinants for Acetylcholine Binding	278
II. Allosteric Modulation of the nAChR Pharmacological Profile	279
F. The nAChR Ion Channel: Stratification, Permeability, Conductance, Rectification and Blockade	282
I. Structure of the Ionic Pore at the Amino Acid Level	282
II. The Ionic Selectivity	284
III. Single Channels Properties of nAChRs	285
IV. Mechanisms Governing the Neuronal nAChR Rectification	288
V. Channel Mutations in Neurological Diseases	289
VI. Open Channel Blockers	290
G. Conclusion	292
References	293

CHAPTER 12

The Functional Diversity of Nicotinic Receptors in the Nervous System: Perspectives on Receptor Subtypes and Receptor Specialization

M.M. FRANCIS and R.L. PAPKE. With 2 Figures	301
A. Introduction	301
B. Functional Domains of Single Subunits	304
C. Calcium and Neuronal nAChR	305
D. Neuronal nAChR Pharmacology	306
E. Changes in Gene Expression with Development	308
F. Functions Served by Neuronal nAChR in the PNS	310
G. Ganglionic Blockers	312
H. Functions Served by Neuronal nAChR in the CNS	315
I. Presynaptic Receptors	317
J. Special Properties of $\alpha 7$ Receptors	323
K. Neuronal nAChR and Developing Therapeutics	325
L. Future Perspectives	329
References	329

CHAPTER 13

Neuronal Nicotinic Receptors and Synaptic Transmission in the Mammalian Central Nervous System

E.X. ALBUQUERQUE, E.F.R. PEREIRA, M. ALKONDON, H.M. EISENBERG, and A. MAELICKE. With 6 Figures	337
A. Introduction	337

B. Experimental Requirements to Monitor Functional Nicotinic Receptors	338
C. Neuronal Nicotinic Receptors Present in Hippocampal Neurons in Culture and in Conventional Slices: Pharmacological and Kinetic Properties	339
I. Nicotinic Receptors in Cultured Hippocampal Neurons ...	339
II. Nicotinic Receptors in Hippocampal Neurons in Conventional Slices	343
D. Neuronal Nicotinic Receptors Control GABAergic and Glutamatergic Synaptic Transmission in the Hippocampus	345
E. Neuronal Nicotinic Receptors Bearing the $\alpha 7$ Subunit Mediate Synaptic Transmission in the CA1 Field of the Hippocampus	348
F. The Role of Choline in Controlling the Function of Nicotinic Receptors Bearing the $\alpha 7$ Subunit – Physiological Relevance	350
G. Concluding Remarks	351
References	353

CHAPTER 14

Properties of Heterologously and Lipid Bilayer Reconstituted Nicotinic Acetylcholine Receptors

C. GOTTI, W. HANKE, and F. CLEMENTI. With 4 Figures	359
A. Introduction	359
B. Experimental Requirements for Bilayer Reconstitution	360
I. Formation of Lipid Bilayers	360
II. Purification of nAChR Subtypes for Reconstitution	360
III. Functional Channel Reconstitution	362
C. Reconstitution of nAChRs	363
I. Muscle-Type Receptor	363
1. $\alpha_2\beta\gamma\delta$ nAChR Channels Expressed in Various Cell Systems	364
a) Calf and Torpedo $\alpha_2\beta\gamma\delta$ nAChR Channel	364
b) Mouse $\alpha_2\beta\gamma\delta$ nAChR Channel	365
2. $\alpha_2\beta\gamma\delta$ nAChR Channel Reconstituted in Lipid Bilayer	365
3. $\alpha_2\beta\gamma\delta$ nAChR Reconstituted in Oocytes	366
4. Desensitisation and Phosphorylation of $\alpha_2\beta\gamma\delta$ nAChR Reconstituted in Lipid Bilayers	367
II. Neuronal-Type Receptor	367
1. Insect α -Bgt Receptors	368
2. Chick $\alpha 7$, $\alpha 8$, and $\alpha 7$ - $\alpha 8$ Subtypes	368
3. Chick $\alpha 6$ Subtype	370
D. Concluding Remarks	372
References	375

CHAPTER 15

Comparison of Native and Recombinant Neuronal Nicotinic Receptors: Problems of Measurement and Expression

L.G. SIVILOTTI, D. COLQUHOUN, and N.S. MILLAR. With 3 Figures	379
A. Introduction	379
B. Methods for Comparing Native and Recombinant Receptors	381
I. Measurements of the Relative Potency of Agonists	381
II. Measurements of the Relative Effectiveness of Antagonists	382
III. Single Channel Measurements	383
IV. Species Differences	384
C. Heterogeneity of Native Receptors	385
I. The Chick Ciliary Ganglion	385
II. Intracardiac Ganglia	388
III. The Rat Superior Cervical Ganglion – Macroscopic Currents	389
IV. Single Channel Studies of Native Ganglionic Receptors	390
V. Antisense Methods on Embryonic Chick Sympathetic Ganglion Neurons	392
D. Heterologous Expression of Recombinant Receptors	393
I. Muscle Nicotinic Receptors	394
II. Glutamate (NMDA-Type) Receptors	395
III. Neuronal Nicotinic Receptors	395
1. Potency Ratios	396
2. Single Channel Properties	397
IV. Receptors with More Than Two Types of Subunit	401
E. Folding, Assembly and Posttranslational Modification	403
F. Conclusions and Prospects	407
References	407

Section IV: Pharmacological Properties

CHAPTER 16

Agonists and Antagonists of Nicotinic Acetylcholine Receptors

S.P. ARNERIC and M.W. HOLLADAY. With 2 Figures	419
A. Introduction	419
B. nAChR Subtype Classification	421
I. Historical Perspective	421
II. Molecular Biology of nAChR Subunits	423
III. Radioligands Used to Identify nAChR Subtypes	424
C. Sites and Modulation of nAChR – Ligand Interaction	425
I. Transition States	425
II. The Nicotinic Pharmacophore	425

III. The ACh Binding Site	426
IV. Channel "Activator" Sites	427
V. Ligand-binding Sites that Inhibit nAChR Function	427
1. Noncompetitive (Negative Allosteric Modulators) Blockers	427
2. Steroid Binding Sites	428
3. Dihydropyridine Binding Site	429
4. Arachidonic Acid Site	430
5. Persistent Modulation of the nAChR Complex	430
D. Pharmacologic Properties of Neuronal nAChRs	431
I. Biochemical and Biophysical Properties of nAChRs Contributing to Pharmacology	431
II. Selective Responsivity of nAChR Subunit Combinations	432
E. SAR of Key Small Molecules Leading to Activation or Inhibition of nAChRs	434
I. Inhibitors	434
1. Peptide Toxins	434
2. Methyllycaconitine (MLA)	435
3. 4-Oxystilbenes	435
4. Other Natural Products	435
II. Positive Allosteric Modulators	436
III. Activators	436
1. ACh	436
2. Nicotine	437
a) Pyridine Ring Modified Analogs	437
b) Pyrrolidine Ring Modified Analogs	438
c) Conformationally Restricted Analogs	438
3. Anabasine and Anabaseine	439
4. <i>Trans-meta</i> -nicotine	439
5. Epibatidine	440
6. Anatoxin	440
7. Pyridyl Ethers: Hybrid Compounds of ACh and Nicotine	441
F. Cholinergic Channel Modulators: Rational for an Alternative Nomenclature	441
G. Perspectives on the Future of Neuronal nAChR Pharmacology	442
References	443

CHAPTER 17

Toxin Antagonists of the Neuronal Nicotinic Acetylcholine Receptor

J.M. MCINTOSH. With 1 Figure	455
A. General Introduction	455
B. Cautionary Note Regarding Species Differences	455

C. Small Molecule Toxins	456
I. General Background	456
II. Plant Toxins	457
1. <i>d</i> -Tuborcurarine	457
2. Dihydro- β -erythroidine	458
3. Methyllycaconitine	459
4. Strychnine	459
III. Marine Toxins	460
1. Neosurugatoxin	460
2. Lophotoxin	460
D. Snake Venom Polypeptides	461
I. General Background	461
II. Snake α -Neurotoxins	461
α -Bungarotoxin	461
III. Snake κ -Neurotoxins	462
κ -Bungarotoxin	462
E. <i>Conus</i> Venom Peptides	464
I. General Background	464
II. α -Conotoxins	465
1. α -Conotoxin MII	465
2. α -Conotoxin ImI	467
3. α -Conotoxin AuIB	469
4. α -Conotoxins PnIA/PnIB and Analogs	469
5. α -Conotoxin EpI	469
6. α -Conotoxin MI	470
F. Conclusion and Future Prospects	470
References	470

CHAPTER 18

Neuronal Nicotinic Acetylcholine Receptors in Non-neuronal Cells, Expression and Renaturation of Ligand Binding Domain, and Modulatory Control by Allosterically Acting Ligands

A. MAELICKE, A. SCHRATTENHOLZ, and E.X. ALBUQUERQUE. With 4 Figures	477
A. Introduction	477
B. Expression of Neuronal Nicotinic Receptors in Mammalian Muscle and Tegumental Cells	478
C. Ectopically Expressed N-terminal Extracellular Domain of nAChR α Subunit	481
D. Modulatory Control of Nicotinic Receptors by Allosterically Acting Ligands	483
E. Allosteric Modulators as Drug Candidates	487
F. Concluding Remarks	490
References	490

CHAPTER 19

Insect Nicotinic Acetylcholine Receptors: Genes, Structure, Physiological and Pharmacological Properties

E.D. GUNDELFINGER and R. SCHULZ. With 4 Figures	497
A. Introduction	497
B. Identified Subunits of Insect nAChRs	498
I. Molecular Cloning of Insect nAChR Genes and cDNAs	498
II. Distribution Pattern of Identified nAChR Subunits in the CNS	504
III. Efforts to Study Subunit Assembly	506
1. Purification of α -Bgt-Binding Receptor Complexes	506
2. Correlation of Cloned Subunits with α -Bgt Binding Sites	507
3. Characterization of Cloned Subunits by Functional Expression in Heterologous Systems	508
C. Physiology and Pharmacology of Native Insect nAChRs	510
I. Electrophysiological Characterization of Insect Neuronal Receptors	511
II. Nicotinic Receptors as Targets for Insecticides	512
D. Nicotinic Receptors of Other Invertebrates	513
E. Conclusions and Perspectives	515
References	516

Section V: The Role of Nicotinic Acetylcholine Receptors in Neuronal Functions

CHAPTER 20

Knockout Mice as Animal Models for Studying Nicotinic Acetylcholine Receptor Function

L.M. MARUBIO and J.-P. CHANGEUX	525
A. Introduction	525
B. Using Knockout Mice as Models	525
C. Knockout of Muscle nAChR Subunits	526
D. The Pharmacology of Neuronal nAChRs Revealed Using Knockout Mice: The Incomplete Story	530
E. Behavioural Analysis of Knockout Mice	533
F. Conclusions and Future Directions	534
References	535

CHAPTER 21

**Noninvasive Exploration of Nicotinic Acetylcholine Receptors
In Vivo**

A. NORDBERG, With 8 Figures	539
A. Introduction	539
I. In Vitro Receptor Binding Studies	539
II. In Vivo and Ex Vivo Studies	540
III. Functional Brain Imaging	540
B. nAChR Ligands for PET and SPECT Studies	541
C. In Vivo [¹¹ C]Nicotine Binding in Human Brain	545
I. Quantification of Nicotine Binding Using k^*_2 Rate Constant	546
D. [¹¹ C]Nicotine Binding in the Brain of Smokers	549
E. PET Studies of nAChRs in Alzheimer's Disease	549
I. Visualization of nAChRs in Alzheimer Patients	549
II. Effect of Drug Treatment on nAChRs in Alzheimer Patients as Studied by PET	550
1. Growth Factors	551
2. Ondansetron	552
3. Cholinesterase Inhibitors	553
F. Conclusions	554
References	555

CHAPTER 22

**Genetic Regulation of Nicotine-Related Behaviors and Brain
Nicotinic Receptors**

J.A. STITZEL, S.S. LEONARD, and A.C. COLLINS	563
A. Introduction	563
B. Human Tobacco Use	563
I. Genetics of Smoking	563
II. Potential Mechanisms for Genetic Influences on Smoking	564
C. Animal Studies of Acute Nicotine Sensitivity	566
I. Genetics of Acute Sensitivity	566
1. Inbred Strain Analyses of Acute Sensitivity to Nicotine	566
2. Analysis of Acute Sensitivity to Nicotine Using Genetic Crosses	567
3. Potential Role for nAChRs in Regulating Acute Sensitivity to Nicotine	568
II. Genetic Influences on the Development of Tolerance to Nicotine	569
1. Comparisons of Tolerance Development Using Inbred Mouse Strains	569

2. Role of Changes in nAChR Numbers in Tolerance	
Development	570
III. Animal Studies of Reinforcing Effects of Nicotine	571
1. Genetics of Oral Self-administration	571
2. Genetic Influences on Conditioned Place Preference	572
D. Tobacco Use and Psychopathology	572
I. Prevalence of Tobacco Use Among the Mentally Ill	572
II. Brain nAChR Binding in Schizophrenics	574
III. Animal Models of Auditory Gating	574
E. Genetics of Nicotinic Receptors and Seizure Disorders	575
I. Human Studies	575
1. The $\alpha 4$ nAChR and Seizure Disorders	575
2. The $\alpha 7$ Gene and Seizure Disorders	576
II. Animal Studies	576
1. Naturally Occurring Seizures	576
2. Nicotine-Induced Seizures	577
F. Summary and Conclusions	579
References	579

CHAPTER 23

The Role of Nicotinic Acetylcholine Receptors in Cognitive Function

E.D. LEVIN. With 3 Figures	587
A. Introduction	587
I. Effects in Humans	587
II. Laboratory Animals	588
III. The Neural Basis of Nicotinic Effects on Cognition	589
IV. Neurotransmitter Interactions	592
B. Therapeutic Possibilities	593
I. Alzheimer's Disease	594
II. Attention Deficit/Hyperactivity Disorder	594
III. Schizophrenia	594
C. Summary and Conclusions	594
References	595

CHAPTER 24

Behavioural Pharmacology and Neurobiology of Nicotine Reward and Dependence

G. DI CHIARA. With 12 Figures	603
A. Introduction	603
I. Defining Dependence and Addiction	603
B. Behavioural Stimulus Effects of Nicotine	606
I. Discriminative Stimulus Effects of Nicotine	607

1. Animal Studies	607
2. Intracerebral Site of the Discriminative Stimulus Effects of Nicotine	610
3. Role of Dopamine in the Discriminative Stimulus Effects of Nicotine	611
4. Nicotine as a Discriminative Stimulus in Humans	614
5. Tolerance to the Discriminative Stimulus Effects of Nicotine	616
6. Summary	617
II. Motivational Stimulus Effects of Nicotine	618
III. Aversive Properties of Nicotine	618
1. Animal Studies	619
2. Human Studies	621
3. Summary	622
IV. Effects of Nicotine on Operant Behaviour	622
1. Intracranial Self-Stimulation	623
2. Effect of Nicotine on Operant Behaviour Maintained by Conventional Reinforcers	624
V. Nicotine Self-Administration	625
1. Pharmacokinetic Factors	625
2. Intravenous Self-Administration	626
3. Nicotine Antagonists on Nicotine Self-Administration in Animals	632
4. Extinction of Nicotine Self-Administration	632
5. Role of Dopamine in Nicotine Self-Administration	636
6. Human Studies	639
7. Reinstatement of Drug Self-Administration as a Model of Craving	639
8. Reinstatement of Intravenous Nicotine Self- Administration	640
9. Oral Nicotine Self-Administration	643
10. Smoking in Animals	644
11. Nicotine Intravenous Self-Administration in Humans	645
12. Nicotine Self-Administration by Nasal Spray in Humans	646
13. Nicotine as the Reinforcing Principle of Tobacco Smoke	648
14. Role of Peripheral and Non-Nicotine Factors in Tobacco Smoking	649
15. Nicotine Self-Administration in Animals as a Model of Human Nicotine Addiction	650
VI. Conditioned Place-Preference	654
C. Locomotion	656
I. Neural Mechanism	659

D. Latent Inhibition and Pre-Pulse Inhibition	660
E. Adaptation to Nicotine	661
I. Tolerance and Sensitization	662
1. Acute Tolerance	662
2. Chronic Tolerance and Sensitization	663
3. Cellular Basis of Adaptation to Nicotine	664
4. Nicotine Receptor Upregulation	665
5. Biochemical Correlates of Nicotine Tolerance in Humans	667
6. Behavioural Tolerance	667
7. Acute and Chronic Tolerance to Nicotine in Humans	668
8. Role of Tolerance to Nicotine in Tobacco Smoking	670
9. Role of Sensitization	672
II. Physiological Dependence on and Withdrawal from Nicotine	672
1. Animal Studies	673
2. Withdrawal from Nicotine in Humans	676
3. Role of Physiological Dependence in Tobacco Smoking	678
F. Neurochemical and Neurophysiological Actions of Nicotine Related to Addiction	680
I. Dopamine	680
1. Expression of nAChRs by Dopamine Neurons	681
2. In Vitro Dopamine Release Studies	682
3. In Vivo and Ex Vivo Studies	684
4. Electrophysiological Effects of Nicotine on Dopamine Neurons	688
5. Role of $\alpha 7$ -Containing nAChRs and of Glutamate	689
6. Adaptive Changes of Dopamine Transmission After Nicotine Exposure	690
7. Desensitization	691
8. Desensitization of Somato-Dendritic nAChRs on Dopamine Neurons	692
9. Inactivation of Somato-Dendritic nAChRs on Dopamine Neurons	692
10. Tolerance and Dependence of Dopamine Transmission	693
11. Sensitization of Dopamine Transmission to Nicotine	698
12. Relationship Between Stimulation of In Vivo Dopamine Transmission by Nicotine and Behaviour	701
II. Noradrenaline	704
III. Serotonin	706

IV. Opioid Peptides	706
V. Amino Acid Transmitters	708
VI. Immediate/Early Genes	708
G. A Model of Nicotine Dependence by Tobacco Smoking	710
References	715

CHAPTER 25

Involvement of Neuronal Nicotinic Receptors In Disease

F. CLEMENTI, J. COURT, and E. PERRY	751
A. Introduction	751
B. Diseases Affecting the Nervous System	751
I. Developmental Disorders	751
1. Tourette's Syndrome	751
2. Schizophrenia	752
II. Age-Independent Disorders	753
1. Epilepsy	753
2. Head Injury	754
3. Depression	754
4. Alcoholism	754
III. Age-Related Degenerative Diseases of the Brain	754
1. Aging	754
2. Alzheimer's and Parkinson's Diseases – Cortical Involvement	755
3. Dementia with Lewy Bodies and Parkinson's Disease – Subcortical Involvement	757
4. Evidence for an Aetiopathological Role for nAChR in Alzheimer's and Parkinson's Diseases Based on Human Pathology and Tobacco Use	758
5. Symptomatic Benefit of Nicotinic Agonists	760
IV. Pathologies in Non-neuronal Tissues and Cells	761
1. Lung Cells	761
a) Small Cell Lung Carcinoma	761
b) Other Lung Cells	762
2. Vascular Smooth Muscle and Endothelial Cells	762
3. Hypertension	763
4. Keratinocytes	764
5. Intestinal Epithelium	765
6. Lymphocytes	765
C. Conclusion	766
References	767

CHAPTER 26

Clinical Aspects of Nicotinic Agents: Therapeutic Applications in Central Nervous System Disorders

P.A. NEWHOUSE and M. KELTON	779
A. Introduction	779
B. Pharmacokinetics and Pharmacodynamics	781
C. Cognitive and Behavioral Effects of Nicotine in Humans	782
D. Potential Clinical Applications	783
I. Movement Disorders	783
1. Parkinson's Disease	783
2. Tourette's Syndrome	785
3. Other Movement Disorders	786
II. Cognitive Disorders	787
1. Nicotinic Involvement in the Regulation of Cognitive Processes	787
2. Alzheimer's Disease	788
a) Studies of Nicotinic Antagonists in Alzheimer's Disease	790
b) Studies of Nicotinic Agonists in Alzheimer's Disease	791
3. Parkinson's Disease	793
4. Nicotinic System Involvement in the Cognitive Disorders of the Cortical Dementias: Synthesis and Therapeutic Model	795
5. Schizophrenia	796
6. Attention Deficit Hyperactivity Disorder	798
III. Other Potential Clinical Applications	799
1. Analgesia	799
2. Cytoprotection	800
3. Smoking Cessation	802
4. Anxiety/Depression	802
5. Epilepsy	803
E. Further Directions	803
References	804
Subject Index	813