

Contents

Section I: Voltage-Dependent Ion Channels

A. Voltage-Dependent Na Channels	1
--	---

CHAPTER 1

Structure and Functions of Voltage-Dependent Na⁺ Channels

K. Imoto. With 3 Figures	3
A. Introduction	3
B. General Architecture	4
C. α Subunit	4
I. Brain Types I, II, and III	7
1. Brain Type II/IIA	7
2. Brain Type I	8
3. Brain Type III	9
II. Skeletal Muscle μ I/SkM1/SCN4A	9
III. Heart I/SkM2/hH1/SCN5A	9
IV. NaCh6 (Rat)/Scn8a (Mouse)/PN4	10
V. PN1/Na _s /hNE-Na/Scn9a	12
1. hNE-Na	12
2. Na _s	12
3. PN1	12
VI. SNS/PN3/NaNG/Scn10a	13
1. SNS/PN3/Scn10a	13
2. NaNG	13
VII. NaN/SNS2	13
VIII. Atypical Sodium Channels	14
1. hNa _v 2.1	14
2. mNa _v 2.3	14
3. SCL-11	14
D. Accessory Subunits	15
I. β 1 Subunit	15
II. β 2 Subunit	15
III. Other Associated Proteins	16
1. TipE	16
2. Ankyrin _G	16

3. AKAP15	17
4. Syntrophins	17
5. Extracellular Matrix Molecules	17
E. Genomic Structure	17
F. Concluding Remarks	17
References	19

CHAPTER 2

Sodium Channel Blockers and Activators

A.O. GRANT. With 3 Figures	27
A. Introduction	27
B. Classification and Structure of Na ⁺ Channels	27
C. Mechanisms of Na ⁺ Channel Blockade by Antiarrhythmic drugs	30
D. Models of Antiarrhythmic Drug Interaction with the Sodium Channel	32
E. The Highly Specific Na ⁺ Channel Blockers TTX and STX	38
F. Peptide Na Channel Blockers: μ Conotoxins	41
G. Na Channel Activators	42
H. Conclusions	45
References	45

B. Voltage-Dependent Ca-Channels

CHAPTER 3

Classification and Function of Voltage-Gated Calcium Channels

J.B. BERGSMAN, D.B. WHEELER, R.W. TSIEN. With 2 Figures	55
A. Generic Properties of Voltage-Gated Ca ²⁺ Channels	55
I. Basic Functional Properties	55
II. Subunit Composition	56
1. α_1	57
2. β	57
3. α_2/δ	58
4. γ	58
B. Classification of Native Ca ²⁺ Channels According to Biophysical, Pharmacological, and Molecular Biological Properties	58
I. Molecular Biological Nomenclature	59
II. Ca _V 1/L-Type Ca ²⁺ Channels	59
III. Ca _V 2	61
1. Ca _V 2.2/N-Type Ca ²⁺ Channels	61
2. Ca _V 2.1/P- and Q-Type Ca ²⁺ Channels	62
3. Ca _V 2.3/R-Type Ca ²⁺ Channels	63

IV. Cav3/T-Type Ca^{2+} Channels	64
V. Note on Pharmacology	65
VI. Evolutionary Conservation of Ca^{2+} Channel Families	65
C. Functional Roles of Ca^{2+} Channels	66
I. Introduction/Subcellular Localization	66
II. Excitation-Contraction Coupling	66
III. Rhythmic Activity	67
1. Pacemaker	67
2. Other	67
IV. Excitation-Secretion Coupling	68
1. Generic Properties	68
2. Peripheral	69
3. Central	70
V. Postsynaptic Ca^{2+} Influx	71
1. Dendritic Information Processing	71
2. Excitation-Expression Coupling and Changes in Gene Expression	72
D. Concluding Remarks	73
References	73

CHAPTER 4

Structure of the Voltage-Dependent L-Type Calcium Channel

F. HOFMANN, N. KLUGBAUER. With 3 Figures	87
A. Introduction	87
B. Subunit Composition and Genes of the Calcium Channel Complex	87
I. Subunit Composition of L-Type Calcium Channels	87
II. Genes	87
1. The α_1 Subunit	87
a) The L-Type α_1 Channels	89
α) The Class S α_1 Gene	89
β) The Class C α_1 Gene	89
γ) The Class D α_1 Gene	89
δ) The Class F α_1 Gene	90
b) The None L-Type α_1 Channels	90
α) The Class A α_1 Gene	90
β) The Class B α_1 Gene	90
γ) The Class E α_1 Gene	90
c) The Low Voltage-Activated α_1 Channels	90
α) The Class G and H Gene	90
2. Auxiliary Subunits of the Calcium Channel	91
a) The $\alpha_2\delta$ Subunit	91
b) The β -Subunit	92
c) The γ Subunit	93

III. Functional Domains of the α_1 Subunit	94
1. The Pore and Ion Selectivity Filter	94
2. Channel Activation	95
3. Channel Inactivation	96
IV. Sites for Interaction with Other Proteins	98
1. Interaction of the α_1 Subunit with the Ryanodine Receptor	98
2. Interaction of the α_1 Subunit with the β Subunit	99
V. Binding Sites for L-Type Calcium Channel Agonists and Antagonists	100
1. The Dihydropyridine Binding Site	100
2. The Phenylalkylamine and Benzothiazepine Binding Site	103
3. Modulation of Expressed L-Type Calcium Channel by cAMP-Dependent Phosphorylation	104
4. Modulation of Expressed L-Type Calcium Channel by Protein Kinase C-Dependent Phosphorylation	106
References	107

CHAPTER 5

Ca²⁺ Channel Antagonists and Agonists

S. ADACHI-AKAHANE, T, Nagao. With 9 Figures	119
A. Ca ²⁺ Channel Antagonists	119
I. Historical Background	119
II. Allosteric Interaction Between Ca ²⁺ Channel Antagonist Binding Sites	121
III. Biophysical and Pharmacological Properties of Ca ²⁺ Channel Antagonists	127
1. Dihydropyridines	128
2. Phenylalkylamines	130
3. Benzothiazepines	131
4. Other Ca ²⁺ Channel Antagonists	132
IV. Binding Sites	133
1. Electrophysiological Identification of Binding Sites for Ca ²⁺ Channel Blockers	133
2. Biochemical Characterization of Drug-Ca ²⁺ Channel Interaction: Photoaffinity Labeling of Ca ²⁺ Channels	135
3. Molecular Biological Characterization of Drug-Ca ²⁺ Channel Interaction: Studies with Experimental Ca ²⁺ Channel Mutants	135
B. Inorganic Blockers	138
C. Natural Toxins and Alkaloids	139
D. Ca ²⁺ Channel Agonists	142
I. DHPs	142
II. Non-DHPs	144

E. Concluding Remarks	144
References	145

C. Voltage-Dependent K-Channels

CHAPTER 6

Overview of Potassium Channel Families: Molecular Bases of the Functional Diversity

Y. KUBO. With 7 Figures	157
A. Introduction	157
B. Primary Structure of the Main Subunit	157
I. 6-Transmembrane (TM) Type	157
II. 2-TM Type	158
III. 1-TM Type	158
IV. 2-Repeat Type	159
C. Heteromultimeric Assembly: Bases of Further Diversity	159
I. Heteromultimer Formation with Other Members of the Same Subfamily	159
1. Kv Channels	159
2. GIRK1,2,4	159
II. Suppression of Functional Expression by Heteromultimeric Assembly	160
III. Heteromultimeric Assembly of Main Subunits of Different Families	160
IV. Assembly with β Subunit	160
V. Assembly with Regulatory Subunits	161
VI. Assembly with Anchoring Protein	162
D. Structural Bases of the Gating Mechanism	162
I. Activation of Kv Channels	162
II. N-Type Inactivation of Kv Channels	163
III. C-Type Inactivation of Kv Channels	164
IV. Activation of IsK	165
E. Structural Bases of the Ion Permeation and Block	165
I. H5 Pore Region	165
II. Re-evaluation	165
III. Inward Rectification Mechanism	166
IV. Direct Structure Analysis	168
F. Structural Bases of Various Regulation Mechanisms	168
I. $G\beta\gamma$	168
II. Block by Cytoplasmic ATP	169
III. Regulation by Phosphorylation	169
IV. Mg^{2+} as a Cytoplasmic Second Messenger	170
V. Regulation by Extracellular K^+	170
VI. Other Mechanisms	170

G. Perspectives	170
References	171

CHAPTER 7

Pharmacology of Voltage-Gated Potassium Channels

O. PONGS, C. LEGROS. With 8 Figures	177
A. Introduction	177
B. Molecular and Functional Organization of the Voltage-Gated Potassium Channels	178
I. Structural Domains in $Kv\alpha$ -Subunits	178
II. Modulatory $Kv\beta$ -Subunits	181
C. Peptide Toxin Binding Sites.....	182
I. Scorpion Toxins	182
II. Snake Toxins	186
III. Sea Anemone Toxins	188
IV. Snail Toxins	189
V. Spider Toxins	190
D. Conclusions	191
References	191

CHAPTER 8

Voltage-Gated Calcium-Modulated Potassium Channels of Large Unitary Conductance: Structure, Diversity, and Pharmacology

R. LATORRE, C. VERGARA, E. STEFANI, L.TORO. With 2 Figures	197
A. Introduction	197
B. Channel Structure	198
C. Auxiliary Subunits	204
D. Calcium Sensitivity and Diversity of BK_{Ca} Channels in Different Cells and Tissues	205
E. Ca^{2+} Sensing Domain(s): The Calcium Bowl	207
F. Origin of Voltage Dependence in BK_{Ca} Channels	208
G. Channel Inactivation	209
H. Metabolic Modulation	210
I. Pharmacology	211
I. BK_{Ca} Channels Blockers	211
1. Toxins	211
2. Organic Blockers	212
a. Tetraethylammonium	212
b. Indole Diterpenes	213
c. General Anesthetics	213
II. BK_{Ca} Channel Activators	213
1. Activators Isolated from <i>Desmodium adscendens</i> : A Medicinal Herb	213

2. Anti-Inflammatory Aromatic Compounds (Fenamates) . . .	214
3. Benzimidazolones	214
4. Phloretin	214
5. Ethanol	214
J. Summary and Conclusions	215
References	215

CHAPTER 9

Classical Inward Rectifying Potassium Channels: Mechanisms of Inward Rectification

C.G. NICHOLS. With 3 Figures	225
A. The Nature of Inward Rectification: Classical Considerations	225
B. The Inward Rectifier Ion Channel Family:	
Two Transmembrane Domain Potassium Channels	227
I. Kir 1 Subfamily	227
II. Kir 2 Subfamily	228
III. Kir 3 Subfamily	228
IV. Kir 4 and 5 Subfamilies	228
V. Kir 6 Subfamily	229
VI. KirD – a New Family of Double-Pored Inward Rectifier Channels?	229
VII. Inward Rectification in Other K ⁺ Channels	229
C. The Mechanism of Inward Rectification:	
Pore Block and Intrinsic	230
D. The Structure of the Kir Channel Pore:	
Binding Sites for Polyamines	231
E. The Structural Requirements for Inward Rectification:	
The Blocking Particles	233
F. The Physiological Significance of Polyamine-Induced Rectification	236
References	236

CHAPTER 10

ATP-Dependent Potassium Channels in the Kidney

G. GIEBISCH, W. WANG, S.C. HEBERT. With 13 Figures	243
A. Introduction	243
B. The Function of ATP-Sensitive K Channels in the Proximal Tubule	243
C. The Function of ATP-Sensitive K Channels in the Thick Ascending Limb (TAL) of Henle's Loop	245
D. The Function of ATP-Sensitive K Channels in the Cortical Collecting Duct (CCD)	247
E. The Regulation of ATP-Sensitive K Channels	248

I. Proximal Tubule	248
II. Thick Ascending Limb of Henle's Loop	249
III. Cortical Collecting Tubules – Apical Membrane of Principal Cells	250
F. Properties of Cloned ATP-Sensitive K Channels (ROMK)	252
I. Channel Structure	252
II. Channel Isoforms and Localization	254
III. Comparison of ROMK with the Native Secretory ATP-Sensitive K Channel	256
IV. The Channel Pore-Rectification	256
V. Regulation by Phosphorylation: Protein Kinase A (PKA) ...	257
VI. Regulation by Phosphorylation: Protein Kinase C (PKC)	259
VII. Regulation by Nucleotides	259
VIII. Regulation by Interaction with Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)	260
IX. Regulation by pH	260
X. Regulation by Phosphoinositides	262
XI. Regulation of ROMK Density in CCD	262
G. ROMK and Bartter's Syndrome	263
References	264

CHAPTER 11

Structure and Function of ATP-Sensitive K⁺ Channels

T. GONOI, S. SEINO. With 5 Figures	271
A. Introduction	271
B. Properties of K _{ATP} Channels in Native Tissues	272
I. Heart	272
II. Skeletal Muscles	273
III. Pancreatic β -Cells	273
IV. Brain	274
V. Smooth Muscles	275
VI. Kidney	275
VII. Mitochondria	276
C. Structure and Functional Properties of Reconstituted K _{ATP} Channels	276
I. The Pancreatic β -Cell Type K _{ATP} Channel	276
1. The Inwardly Rectifying K ⁺ Channel Subfamily Kir6.0	276
2. The Sulfonylurea Receptor SUR1	277
3. Reconstitution of the Pancreatic β -Cell Type K _{ATP} Channel	281
II. The Cardiac and Skeletal Muscle Type K _{ATP} Channel	283
1. The Sulfonylurea Receptor SUR2A	283

2. Reconstitution of the Cardiac and Skeletal Muscle Type K_{ATP} Channel	283
III. The Smooth Muscle Type K_{ATP} Channel	283
1. The Sulfonylurea Receptor SUR2B	283
2. Reconstitution of the Smooth Muscle Type K_{ATP} Channel	283
IV. The Vascular Smooth Muscle Type K_{ATP} Channel	284
1. Reconstitution of the Vascular Smooth Muscle Type K_{ATP} Channel	284
D. Physical Interaction and Stoichiometry of the Pancreatic β -Cell Type K_{ATP} Channel Subunits	284
I. Physical Interaction Between the SUR1 Subunit and the Kir6.2 Subunit	284
II. Subunit Stoichiometry of the SUR1/Kir6.2 Channel	285
E. Domains Conferring Sensitivities to the Nucleotides and Pharmacological Agents	285
I. ATP-Sensitivity	285
II. Nucleotide Diphosphate (NDP)-Sensitivity	286
III. Diazoxide-Sensitivity	286
IV. Sulfonylurea-Sensitivity	287
V. Mg^{2+} - and Spermin-Sensitivity	287
VI. Phentolamine-Sensitivity	287
VII. G-Protein Sensitivity	287
F. Pathophysiology of the Pancreatic β -Cell K_{ATP} Channel	288
I. Persistent Hyperinsulinemic Hypoglycemia of Infancy	288
II. Transgenic Mice	288
G. Conclusions	288
References	289

CHAPTER 12

G Protein-Gated K^+ Channels

A. INANOBE, Y. KURACHI*. With 11 Figures	297
A. Introduction	297
B. Acetylcholine-Activation of Muscarinic K^+ Channels	298
I. G Protein's Cyclic Reaction	299
II. Positive Cooperative Effect of GTP on the Muscarinic K^+ Channel Activity	302
III. Incorporation of Receptor-G Protein Reaction to the Model of K_{ACh} Channel	304
C. Molecular Analyses of G Protein-Gated K^+ Channels	305
I. Cloning of Inwardly Rectifying K^+ Channels and Kir Subunits for G Protein-Gated K^+ Channels	305
II. GIRK Subfamily	307

III. Expression of GIRK Channels	309
IV. Tetrameric Structure of Kir Channels	312
V. Molecular Mechanism Underlying Activation of the G Protein-Gated K ⁺ Channels by $\beta\gamma$ Subunits of G Protein ...	313
1. The G Protein $\beta\gamma$ Subunit-Binding Domains in GIRK Subunits	313
2. Putative Mechanism Underlying the G Protein $\beta\gamma$ Subunit-Induced Activation of the G Protein-Gated K ⁺ Channels	316
3. PIP ₂ -Mediation of G $\beta\gamma$ -Activation of K _G Channels	316
VI. The Possible Role of G Protein α Subunits in the G Protein-Gated K ⁺ Channel Regulation	317
1. Possibility of Microdomain Composed of Receptor, G Protein and the G Protein-Gated K ⁺ Channel	317
2. Specificity of Signal Transduction Based on the Receptor/G Protein/ G Protein-Gated K ⁺ Channel Interaction	317
D. Localization of the G Protein-Gated K ⁺ Channel Systems in Various Organs	318
I. Cardiac Atrial Myocytes	319
II. Neurons	321
III. Endocrine Cells	322
E. <i>Weaver</i> Mutant Mice and GIRK2 Gene	323
F. Conclusions	323
References	324

CHAPTER 13

Potassium Channels with Two Pore Domains

F. LESAGE, M. LAZDUNSKI. With 3 Figures	333
A. K ⁺ Channels with One Pore Domain	333
B. K ⁺ Channels with Two Pore Domains	334
I. TWIK, the Archetype of a Novel Structural Class of K ⁺ Channel	334
1. Cloning and Gene Organization	334
2. Functional Expression	335
3. Structure of the Channel	337
II. Related K ⁺ Channels in Mammals	337
1. TREK is an Unusual Outward Rectifier K ⁺ Channel	338
2. TASK is an Open Rectifier Channel Highly Sensitive to External pH	339
3. TRAAK Forms K ⁺ Channels Activated by Unsaturated Fatty Acids	340
III. Related Channels in Worm, Fly, Yeast, and Plant	340

C. Concluding Remarks	341
References	343

CHAPTER 14

Cardiac K⁺ Channels and Inherited Long QT Syndrome

M.-D. DRICI, J. BARHANIN. With 3 Figures	347
A. Long QT Syndromes	347
B. <i>HERG</i> and LQT2	348
I. The <i>HERG</i> Gene	348
II. I _{Kr} Current and LQT2	348
C. KvLQT1/IsK, LQT1, and LQT5	352
I. <i>KVLQT1</i> and <i>ISK</i> Genes	352
II. I _{Ks} Current, LQT1, and LQT5	352
III. Physiological Role of I _{Ks} in Cardiac Repolarization	355
D. Pharmacological Considerations in the Acquired LQTS	356
I. Determinants of Cardiac Repolarization	356
II. Pharmacological Modulation of Cardiac Repolarization and Acquired Long QT Syndromes	357
E. Conclusion	358
References	359

Section II: Ligand Operated Ion Channels

CHAPTER 15

Gating of Ion Channels by Transmitters: The Range of Structures of the Transmitter-Gated Channels

E.A. BARNARD. With 4 Figures	365
A. Introduction: The Scope of the Transmitter-Gated Channel Class	365
B. Structural Elements of the Membrane Domains of the Transmitter-Gated Channels	366
I. Transmembrane Domains	366
II. The α -Helix in Channel Transmembrane Domains	367
III. Supporting Transmembrane Structures	371
IV. Pore Loops (P-Domains)	371
C. The Subclasses of the Transmitter-gated Channels	373
I. The TGCs are in Completely Diverse Superfamilies	373
II. The Cys-Loop Receptors	374
III. Glutamate-Gated Cation Channels	378
IV. Channels Structurally Related to Voltage-Gated Channels	379
1. Cyclic Nucleotide-Gated Channels	379

2. Inositol Trisphosphate (IP ₃) Receptors	380
3. Ryanodine Receptors	380
4. Vanilloid Receptors and Store-Operated Channels	380
V. Channels Topologically Related to Epithelial Na ⁺ Channels	381
1. P2X Channels	381
2. Proton-Gated Channels	381
3. Peptide-Gated Channels	383
VI. Channels Related to Inward Rectifier K ⁺ Channels	383
1. Nucleotide-Sensitive K ⁺ Channels	383
2. Nucleotide-Dependent K ⁺ Channels	384
3. Channels Containing Bi-Functional Kir Subunits	384
VII. Channels Related to ATP-Binding Transporters	385
VIII. Channels Related to Neurotransmitter Transporters	385
D. Conclusion	386
References	386

CHAPTER 16

Molecular Diversity, Structure, and Function of Glutamate Receptor Channels

M. MISHINA. With 2 Figures	393
A. Introduction	393
B. Structure and Molecular Diversity of the GluR Channel	393
I. Subunit Families and Subtypes	393
II. Primary Structure and Transmembrane Topology Model ...	394
C. AMPA Subtype	395
I. AMPA-Type Subunits	395
II. GluR2 Subunit and Ca ²⁺ Permeability	396
III. Q/R Site as a Determinant of Channel Properties	396
IV. Phosphorylation	397
V. Autoimmune Disease	397
VI. GRIP, an Associated Protein	397
D. Kainate Subtype	397
E. NMDA Subtype	398
I. Heteromeric Nature of NMDA Receptor Channels	398
II. Dynamic Variations of the Distribution of the Subunits ...	399
III. Splice Variants	400
IV. Channel Pore and Gating	401
V. Agonist Binding	402
VI. Phosphorylation	403
VII. Modulation	403
VIII. Synaptic Plasticity, Learning, and Neural Development ...	404
IX. Associated Post-Synaptic Proteins	404

F. Additional Members of the GluR Channel Family	405
I. GluR δ Subfamily	405
II. GluR χ Subfamily	406
References	406

CHAPTER 17

Glutamate Receptor Ion Channels: Activators and Inhibitors

D.E. JANE, H.-W. TSE, D.A. SKIFTER, J.M. CHRISTIE, D.T. MONAGHAN. With 15 Figures	415
A. Introduction	415
I. Receptor Classification	415
II. Molecular Biology of AMPA, Kainate, and NMDA Receptors	416
B. Pharmacology of AMPA Receptors	417
I. AMPA Receptor Agonists	417
II. Competitive AMPA Receptor Antagonists	419
1. Quinoxalinediones and Related Compounds	419
2. Decahydroisoquinolines	423
3. Isoxazoles	425
4. Phenylglycine and Phenylalanine Analogues	426
III. Benzodiazepine Analogues as Non-Competitive AMPA Receptor Antagonists	427
IV. Positive Allosteric Modulators	428
V. Channel Blockers	429
C. Kainate Receptor Pharmacology	431
I. Kainate Receptor Agonists	431
II. Competitive Kainate Receptor Antagonists	433
1. Quinoxalinediones and Related Compounds	433
2. Decahydroisoquinolines	433
3. Positive Allosteric Modulators Acting on Kainate Receptors	434
D. Therapeutic Potential of AMPA and Kainate Receptor Ligands	434
E. Pharmacology of NMDA Receptors	436
I. Therapeutic Considerations	436
II. The NMDA Receptor Glutamate Recognition Site	438
1. Glutamate Recognition Site Radioligands	438
2. Glutamate Binding Site Agonists	439
3. Glutamate Recognition Site Competitive Antagonists ...	440
4. Antagonist Specificity for Subtypes of Glutamate Recognition Sites	443
III. NMDA Receptor Channel Blockers	444
1. Channel Blocker Pharmacology	444

2. Channel Blocker Receptor Subtype Selectivity	446
IV. The NMDA Receptor Glycine Recognition Site	447
1. Radioligand Binding and Functional Characteristics of the Glycine Receptor	447
2. NMDA Receptor Glycine Site Agonists	449
3. NMDA Receptor Glycine Site Antagonists	450
V. Allosteric Modulatory Sites on the NMDA Receptor	452
1. Polyamines	452
2. Spider and Wasp Toxins	453
3. Ifenprodil and Other NR2B Selective Compounds	453
4. Proton Inhibition	455
5. Zinc	455
F. Conclusions	456
References	459

CHAPTER 18

Structure, Diversity, Pharmacology, and Pathology of Glycine Receptor Chloride Channels

R.J. HARVEY, H. BETZ. With 2 Figures	479
A. Introduction	479
I. The Neurotransmitter Glycine	479
B. Structure and Diversity of Glycine Receptor Channels	479
I. GlyRs are Ligand-Gated Ion Channels of the nAChR Superfamily	479
II. Glycine Receptor Heterogeneity	480
III. The GlyR Ligand-Binding Domain	482
IV. Determinants of Ion Channel Function	483
V. Clustering of GlyRs by the Anchoring Protein Gephyrin	484
C. Pharmacology of Glycine Receptors	484
I. Strychnine is a Selective GlyR Antagonist	484
II. Amino Acids and Piperidine Carboxylic Acid Compounds	486
III. Antagonism by Picrotoxinin, Cyanotriphenylborate, and Quinolinic Acid Compounds	487
IV. Potentiation of GlyR Function by Anesthetics, Alcohol and Zn^{2+}	488
D. Pathology of Glycine Receptors	489
I. Mouse Glycine Receptor Mutants: <i>Spastic</i> , <i>Spasmodic</i> , and <i>Oscillator</i>	489
II. Mutations in GLRA1 Underlie the Human Hereditary Disorder Hyperekplexia	490
E. Conclusions	491
References	492

CHAPTER 19

GABA_A Receptor Chloride Ion Channels

R.W. OLSEN, M. GORDEY. With 4 Figures	499
A. GABA _A Receptors: Physiological Function, Molecular Structure, Pharmacological Subtypes	499
B. Activators and Inhibitors of GABA _A Receptors	502
I. GABA Site	502
1. Agonists	502
2. Antagonists	504
II. The Picrotoxin Site	505
III. Benzodiazepine Site Ligands	506
IV. Barbiturates and Related Drugs	509
V. Neuroactive Steroids	511
VI. General Anesthetics: Propofol, Volatile Agents, and Alcohols	511
VII. Miscellaneous Agents	512
C. Discussion	512
References	512

CHAPTER 20

P2X Receptors for ATP: Classification, Distribution, and Function

R.J. EVANS. With 1 Figure	519
A. Introduction	519
B. Molecular Biology of P2X Receptors	519
I. A New Structural Family of Ligand Gated Ion Channels ...	520
II. The Extracellular Loop/Ligand Binding Site	520
III. Transmembrane Domains; Location of the Ionic Pore	522
1. Intracellular N and C Termini	523
2. Genomic Organisation, Human P2X Receptors and Chromosomal Location	523
C. Distribution of P2X Receptors	523
I. P2X ₁ Receptors	524
II. P2X ₂ Receptors	524
III. P2X ₃ Receptors	525
IV. P2X ₄ Receptors	525
V. P2X ₅ Receptors	526
VI. P2X ₆ Receptors	526
VII. P2X ₇ Receptors	526
D. Functional Properties of P2X Receptors	527
I. General Features of P2X Receptors	527
1. P2X ₁ Receptors	528
2. P2X ₂ Receptors	528
3. P2X ₃ Receptors	529

4. P2X ₂ /P2X ₃ Heteromeric Receptors	529
5. P2X ₄ Receptors	529
6. P2X ₅ Receptors	530
7. P2X ₆ Receptors	530
8. P2X ₇ Receptors	530
II. Modulation of P2X Receptors	531
III. Native P2X Receptor Phenotypes; Molecular Correlates	532
1. Smooth Muscle	532
2. Sensory Neurons	533
3. Peripheral Neurons	534
4. Brain	534
5. Immune/Blood Cells	534
6. Salivary Gland	535
E. Future Directions	535
References	535

CHAPTER 21

The 5-HT₃ Receptor Channel: Function, Activation and Regulation

J.L. YAKEL. With 1 Figure	541
A. Introduction	541
B. Receptor Distribution	542
C. Molecular Structure	542
I. Sequence, Assembly, and Splice Variants	542
II. Gene Structure	544
III. Developmental Regulation	544
IV. Homo-Oligomeric Vs Hetero-Oligomeric Assembly	544
D. Function in the Nervous System	545
I. Presynaptic Role and Neurotransmitter Release	545
II. Postsynaptic Role	546
III. Physiological Properties	547
1. Receptor Activation	547
2. Single-Channel Properties	547
3. Desensitization	548
4. Ion Permeation and Pore Structure	549
5. Rectification and Voltage-Dependence	550
IV. Modulation, Synaptic Plasticity, and Learning and Memory	551
E. Pharmacological Properties	552
I. 5-HT ₃ R Ligands: Agonists and Antagonists	552
II. 5-HT ₃ R Ligand Binding Site	553
F. Allosteric Regulation	554
I. Alcohols	554
II. Anesthetics	554

III. 5-Hydroxyindole	555
G. Conclusion	555
References	556

CHAPTER 22

Cyclic Nucleotide-Gated Channels:

Classification, Structure and Function, Activators and Inhibitors

M.E. GRUNWALD, H. ZHONG, K.-W. YAU. With 2 Figures	561
A. Introduction	561
B. Structure	562
C. Ion Permeation Properties	563
D. Cyclic-Nucleotide Binding and Channel Gating	565
E. Modulations	568
I. Ca^{2+} -Calmodulin	568
II. Ca^{2+}	569
III. Phosphorylation	569
IV. Transition Metals	570
V. Sulfhydryl Reagents	570
VI. Protons	571
VII. Other Modulators	571
F. Blockers	571
G. Conclusions	572
References	573

Section III: Miscellaneous Ion Channels – Intracellular Ca Release Channels

CHAPTER 23

Regulation of Ryanodine Receptor Calcium Release Channels

M. ENDO, T. IKEMOTO	583
A. Introduction	583
B. Molecular Structure and Function of RyR	584
C. Different Modes of Opening of RyR1 Calcium Release Channel	585
D. Activators of RyRs	588
I. Calcium, Strontium, and Barium Ions	589
II. Adenine Compounds	590
III. Caffeine and Related Compounds	590
IV. Ryanodine and Ryanoid	591
V. Halothane and Other Inhalation Anesthetics	592
VI. Oxidizing Agents and Doxorubicin	593

VII. Cyclic ADP-Ribose	593
VIII. Calmodulin and Other Endogenous Modulatory Proteins	593
IX. Imperatoxin Activator	594
X. Clofibrilic Acid	594
XI. Miscellaneous Activators	595
E. Inhibitors of RyRs	595
I. Magnesium Ion	595
II. Procaine and Other Local Anesthetics	596
III. Ruthenium Red	596
IV. Dantrolene	596
F. Closing Remarks	596
References	597

CHAPTER 24

Regulation of IP₃ Receptor Ca²⁺ Release Channels

M. IINO. With 1 Figure	605
A. Introduction	605
B. Molecular Structure and Function of IP ₃ R	605
C. Physiological Agonists and Modulators of IP ₃ R	607
I. IP ₃	607
II. Ca ²⁺	609
III. ATP	610
IV. Phosphorylation	610
D. Activators of IP ₃ R	611
I. IP ₃ Analogues	611
II. Caged IP ₃	612
III. Thimerosal	612
IV. Immunophilin Ligands	613
V. Mn ²⁺	613
E. Inhibitors of IP ₃ R	613
I. Heparin	613
II. Xestospongine	614
III. Caffeine	614
IV. Cyclic ADP-Ribose	614
F. Comparison of Pharmacology Between IP ₃ R and RyR	615
G. Spatio-Temporal Patterns of IP ₃ R-Mediated Ca ²⁺ Signals	615
H. Perspectives	617
References	617

CHAPTER 25

Ca²⁺-Activated Non-Selective Cation Channels

J. TEULON	625
-----------------	-----

A. Introduction	625
B. Tissue Distribution	625
C. Conductive Properties	628
I. Unit Conductance and Voltage Dependence	628
II. Ion Selectivity	629
III. Ca-Permeable, Ca-Dependent Cation Channels: A Subtype of the NSC _{Ca} Channel?	630
D. Blockers and Pharmacological Stimulators	630
I. Blockers	630
II. Pharmacological Stimulators	632
E. Intracellular Regulatory Elements	633
I. Calcium Sensitivity	633
II. Inhibition by Intracellular Nucleotides	633
III. Tonic Influence of Intracellular ATP	635
IV. Stimulatory Effects of Intracellular Cyclic Nucleotides	635
V. Other Regulators: Internal pH and Oxidation	635
F. Phosphorylation-Dependent Regulation	636
I. Regulation via Protein Kinase A	636
II. Effects of Other Protein Kinases	637
G. Dependence on Hypertonicity	637
H. Agonist-Mediated Control of NSC _{Ca} Channels	638
I. Physiological Role	639
I. Excitable Cells: "Voltage Signal"	640
II. Exocrine Glands: Participation in Cl ⁻ Transport	641
III. Other Epithelia: Speculative Functions	642
References	643
Subject Index	651

Pharmacology of Ionic Channel Function: Activators and
Inhibitors

Endo, M.; Kurachi, Y.; Mishina, M. (Eds.)

2000, XXXI, 662 p., Hardcover

ISBN: 978-3-540-66127-6