

Pharmacology of GABA and Glycine Neurotransmission

Contributors

B.E. Alger, J. Auta, E.A. Barnard, D. Belelli, B. Bettler
H. Betz, J. Bormann, N.G. Bowery, N.J. Brandon, J.E. Clark
W.A. Clark, E. Costa, S.J. Enna, A. Feigenspan, A. Guidotti
S.C. Harney, R. Adron Harris, N.L. Harrison, R.J. Harvey
B.K. Kanner, K. Kaupmann, H.Y. Kim, M.D. Krasowski
J.J. Lambert, F.E.N. Le Beau, B.S. Meldrum, H. Möhler
S.J. Moss, R.W. Olsen, J.A. Peters, P. Schloss, T.G. Smart
P. Thomas, P. Whiting

Editor

Hanns Möhler



Springer

Contents

Section I: Physiology of the Neurotransmitters GABA and Glycine

CHAPTER 1

Physiology of the GABA and Glycine Systems

B.E. ALGER and F.E.N. LE BEAU. With 8 Figures	3
A. Introduction	3
B. Subtypes of Interneurons	4
I. Electrophysiological Properties of Interneurons	5
1. Voltage-Dependent Channels	6
2. Ligand-Gated Channels	8
C. Physiological Responses Mediated by Inhibitory Neurotransmitters	10
I. Membrane Effects of GABA and Glycine	10
II. Depolarizing GABA and Glycine Responses	12
1. Depolarizing GABA and Glycine Responses in Young Tissue	12
2. Depolarizing GABA _A Responses in Adult Tissue	13
III. Membrane Potential Changes Caused by GABA in Unimpaired Cells	14
D. Miniature Inhibitory Postsynaptic Currents	15
I. Saturation of Receptor Patches by Quantal Release	15
II. Co-Release of GABA and Other Transmitters	19
1. GABA and Glycine	19
2. Co-Release of GABA and ATP	19
III. Multiquantal Release	20
IV. Tonic Inhibition	23
E. Dendritic Inhibition	24
I. Control of Dendritic Electroresponsiveness	24
II. Dendrodendritic Inhibition	25
III. Back-Propagating Action Potentials	26
IV. Control of Persistent Cation Currents	28

F. Somatic-Axonal Inhibition	28
I. Conduction Block Along the Preterminal Axon	28
II. Depolarization-Induced Suppression of Inhibition (DSI)	30
III. Autoreception and Inhibition	33
1. Autaptic Transmission	33
2. Preterminal Extrasynaptic Receptors	33
G. GABA _B Responses	34
I. Postsynaptic Inhibition	34
II. Presynaptic Inhibition	36
1. GABA _B Autoreceptor Activation	36
2. Mechanism of Presynaptic GABA _B Inhibition	37
III. GABA _B Enhancement of Synaptic Activity	38
H. Response Plasticity and IPSPs	39
I. Short-Term Plasticity of Interneuron Output	39
II. Balance Between Excitation and Inhibition	41
III. The Roles of IPSPs in Regulating Plasticity at Excitatory Synapses	42
1. LTD of GABA _A ergic IPSPs in Hippocampus	42
2. LTD of GABA _A ergic IPSPs in Cerebellum	43
IV. Long-Lasting Enhancement of GABA _A IPSPs	45
1. LTP of GABA _A ergic IPSPs	45
2. LTP of Glycinergic IPSPs	46
3. Long-Lasting Enhancement of IPSPs – Not LTP	47
V. Target-Cell Specificity of Action	47
VI. Facilitation of LTD Induction at Other Synapses by IPSP Depression	48
I. Synaptic Inhibition and the Generation of Rhythmic Firing Patterns in Populations of Cells	49
I. Gamma Oscillations	50
II. Theta Rhythms	51
III. Single-Unit Studies In Vivo	51
IV. Thalamic Rhythms	52
V. Depolarizing GABA _A Responses and Rhythmic Firing	53
VI. Hypersynchrony and Pathology	54
VII. Control of Rhythmic Firing Through Inhibition of Gap Junctional Connections	55
J. The Role of Inhibition in Sensory Processing	56
I. Receptive Field Shape	56
II. Dynamic Modulation of Receptive Fields	57
1. Deafferentation Plasticity	57
2. Activity-Dependent Receptive Field Modifications	58
3. Glycine and Motor Reorganization	59
K. Conclusions	60
References	60

Section II: Pharmacology of the GABA System

GABA_A Receptors

CHAPTER 2

The Molecular Architecture of GABA_A Receptors

E.A. BARNARD. With 2 Figures	79
A. Repertoire of Subunit Types	79
I. Structural Diversity and Uniformity	79
II. Subfamilies of Subunits	82
B. The Subunit Number per Receptor Molecule	83
C. Subunits Within the Pentamer	84
I. Two Subunit Pools for Receptor Assembly	84
II. A Constrained Combinatorial System for the Receptor Compositions	85
D. Stoichiometry Within the Pentamer	88
I. Co-occurrence of Two Isoforms of One Subunit Type	88
II. Possibilities for Subunit Stoichiometry	89
E. GABA _A Receptors Containing Other Types of Subunits	89
I. The δ Subunit	90
II. The ϵ Subunit	90
III. The π Subunit	91
IV. The θ Subunit	91
F. The ρ Subunits	91
G. Conclusions on the Subtypes	92
References	94

CHAPTER 3

Functions of GABA_A-Receptors: Pharmacology and Pathophysiology

H. MÖHLER. With 3 Figures	101
A. Introduction	101
B. Pharmacology of GABA _A -Receptor Subtypes	101
I. Benzodiazepine Actions at GABA _A -Receptor Subtypes	101
1. Distinction of Receptor Subtypes by Point Mutations ...	101
2. Sedation and Receptor Subtypes	103
3. Amnesia and Receptor Subtypes	103
4. Anticonvulsant Activity and Receptor Subtypes	104
5. Myorelaxation, Potentiation and Receptor Subtypes	104
6. Anxiolytic Activity and Receptor Subtypes	104
7. Strategies for Drug Design	105
II. Ethanol and GABA _A Receptor Subtypes	105
III. Anaesthetics and Pentobarbital	106

C. GABA _A -Receptor Mutants as Models for Disease	106
I. Anxiety-Behaviour and Bias for Threat Cues	106
1. Genetically Defined Animal Model of Anxiety	107
2. Enhanced Reactivity to Natural Aversive Stimuli	107
3. Learned Aversive Stimuli	108
4. Pathophysiology of Anxiety Disorders	108
II. Craniofacial Development.	110
III. Angelman's Syndrome	110
IV. Desynchrony of Neuronal Oscillations	110
D. Limitations of the Gene Inactivation Approach	110
I. Adaptation	111
II. Severity of Impairment	111
III. Marker Genes	111
IV. Strain Differences	112
References	112

CHAPTER 4

Steroid Modulation of GABA_A Receptors

J.J. LAMBERT, J.A. PETERS, S.C. HARNEY, and D. BELELLI.

With 2 Figures	117
A. Introduction	117
B. Structure Activity Relationship for Steroids at the GABA _A Receptor	120
I. Enantioselectivity of Steroid Action	122
II. The Ring System	122
III. C2 Substitution	122
IV. C3 Substitution	124
V. C5, C10 or C11 Substitution	126
VI. The C17 Side Chain	126
VII. C20 Substitution	127
VIII. C21 Substitution	127
IX. Summary	127
C. Neurosteroid Binding Site Heterogeneity and the Influence of GABA _A Receptor Subunit Composition upon Neurosteroid Action	128
I. α Subunits	128
II. β Subunits	130
III. γ Subunits	130
IV. The δ Subunit	130
V. The ϵ Subunit	130
VI. Summary	131
D. Molecular Mechanism of Neurosteroid Action	131
E. Neurosteroid Effects on Synaptic Transmission	132

F. Concluding Remarks	134
References	135

CHAPTER 5

Allosteric Modulation of GABA_A Receptor Function by General Anesthetics and Alcohols

M.D. KRASOWSKI, R.A. HARRIS, and N.L. HARRISON.

With 5 Figures	141
A. Introduction	141
B. What is a General Anesthetic?	141
C. Special Considerations for Alcohol	143
D. Overview of Ligand-Gated Ion Channels	143
E. GABA _A and Glycine Receptors	144
F. Pharmacological Criteria for a Reasonable General Anesthetic/ Alcohol Target Site	146
I. What is the "Clinically Relevant Concentration" for a General Anesthetic?	147
II. Anatomical Location	148
III. Stereoselectivity	148
IV. Hydrophobicity	150
V. Alcohol Cutoff	150
G. Experimental Approaches to Studying General Anesthetic and Alcohol Actions at the GABA _A Receptors	151
H. Actions of General Anesthetics at GABA _A Receptors	152
I. Volatile Anesthetics and Anesthetic Gases	155
J. Intravenous Anesthetic Agents	157
K. Alcohols	158
L. GABA _A and Glycine Receptors and Ethanol Action	158
M. Cutoff	160
N. Discussion and Future Directions	161
References	162

CHAPTER 6

Anticonvulsants Acting on the GABA System

B.S. MELDRUM and P. WHITING. With 3 Figures	173
A. Introduction	173
I. Role of GABA and GABA Receptors in Epilepsy	173
1. Developmental Changes in GABA _A Receptor Effects	174
II. Mechanism of Action of Antiepileptic Drugs	175
B. GABA Transporters and Tiagabine	175

I. Effects of Other Anti-Epileptic Drugs on GABA-Transporters	178
II. Changes in GABA Transporters in Epilepsy	179
C. Vigabatrin and Inhibition of GABA-Transaminase	179
D. Anticonvulsants Acting Through the GABA _A Receptor	180
I. Benzodiazepines	181
II. Barbiturates	181
III. Steroids	182
IV. Loreclezole	182
V. Topiramate	183
VI. Chlormethiazole	183
E. Alterations in GABA Receptors in Epilepsy	183
I. Alterations in the Expression of GABA _A Receptors in Animal Models of Seizure.	183
II. GABA _A Receptors and Absence Epilepsy	186
III. Alterations in GABA Levels and GABA _A Receptors in Human Epilepsy	187
F. GABAergic Agents in Status Epilepticus	187
G. Conclusions: Future Prospects for Anti-Epileptic Drugs Acting on GABAergic Transmission	188
References	188

CHAPTER 7

Heterologous Regulation of GABA_A Receptors:

Protein Phosphorylation

T.G. SMART, P. THOMAS, N.J. BRANDON, and S.J. MOSS.

With 4 Figures	195
A. Introduction	195
B. Physiological Role of GABA _A Receptors	196
C. Molecular Structure of GABA _A Receptors	196
I. GABA _A Receptor Subunit Families	196
II. Domain Structures and Alternative Splicing	197
III. Subunit Heterogeneity and Co-Assembly	198
D. Consensus Sites for Protein Phosphorylation	198
E. Identifying Phosphorylation Sites Within GABA _A Receptor Subunits	199
I. Phosphorylation of Neuronal GABA _A Receptors	199
II. Consensus Phosphorylation Sites in the Large Intracellular Domains	200
III. Phosphorylation of Recombinant GABA _A Receptors	201
1. Use of Fusion Proteins	201
2. Use of Receptor Subunits	201
F. GABA _A Receptor Phosphorylation: Consequences for Ion Channel Function	202

I. cAMP-Dependent Protein Kinase	202
1. Native Neurones	202
2. Recombinant Receptors	203
II. cGMP-Dependent Protein Kinase	207
III. Ca ²⁺ /Phospholipid Dependent Protein Kinase	207
IV. Ca ²⁺ /Calmodulin-Dependent Protein Kinase II and Ca ²⁺ -Dependent Phosphatases	210
V. Tyrosine Kinases	212
1. GABA _A Receptor: Response Rundown and Washout ...	213
G. Regulation of GABA _A Receptor Cell Surface Expression	214
H. Conclusion	217
References	218

CHAPTER 8

Tolerance and Dependence to Ligands of the Benzodiazepine Recognition Sites Expressed by GABA_A Receptors

E. COSTA, J. AUTA, and A. GUIDOTTI. With 2 Figures	227
A. A Mechanistic Hypothesis on the Tolerance and Dependence to the Ligands of <i>Benzodiazepine Recognition Sites</i> (BZ-RS) Expressed by GABA _A Receptors	227
B. Tools to study changes in GABA _A receptor subunit assembly	228
C. Limitations in Interpreting Studies of GABA _A Receptor Chimerae With and Without Single Amino Acid Mutations	229
D. Characterization of BZ-RS Ligands Endowed with Anxiolytic and Anticonvulsant Actions	230
E. Can the Subunit Expression Modification Associated with BZ Tolerance Explain the Decreased Intrinsic Activity of Full Positive-Allosteric Modulators at GABA _A Receptors?	235
I. Changes in GABA Receptor Subunit Assembly	235
1. Studies on Ligand Binding to BZ-RS	235
2. Changes in GABA _A Receptor Subunit mRNA Expression	236
3. Changes in GABA _A Receptor Subunit Expression	238
II. GABA _A Receptor Subunit Allosteric Uncoupling	239
F. Are Changes in GABA _A Receptor Subunit Assembly Relevant to BZ Dependence?	240
G. Development of Tolerance and Dependence Liability After Long-Term Treatment with Selective-Positive-Allosteric Modulators of GABA _A Receptors	242
I. Zolpidem	242
II. Abecarnil	242
H. Lack of Tolerance or Dependence Following Long Term Treatment with Partial-Positive-Allosteric BZ-RS Ligands	243

I. Imidazenil is Devoid of Tolerance and Dependence	
Liability in Rodents	244
II. Imidazenil is Devoid of Tolerance and Dependence	
Liability in Monkeys	245
References	247

CHAPTER 9

GABA_A Receptors and Disease

H.Y. KIM and R.W. OLSEN	251
A. Introduction	251
B. Diseases of Development and GABA _A Receptors	252
C. Diseases of Adult and GABA _A Receptors	254
I. GABA _A Receptor Function in Adult Epilepsy	254
II. GABA _A Receptor Function in Anxiety	257
III. GABA _A Receptor Function in Alcoholism	258
D. Conclusion	260
References	261

CHAPTER 10

GABA_C Receptors: Structure, Function and Pharmacology

J. BORMANN and A. FEIGENSPAN. With 7 Figures	271
A. Introduction	271
B. Structure of GABA _C Receptors	272
I. Cloning of Vertebrate ρ -Subunits	272
II. Subunit Composition of GABA _C Receptors	272
C. Neuronal Localization	272
D. Functional Properties of GABA _C Receptors	274
I. Identification of GABA _C Receptors	274
II. GABA Affinity and Ion Selectivity	274
III. Single Channel Characteristics	276
IV. Pore Size	276
V. Desensitization	277
E. Pharmacology	278
I. GABA _C Agonists	278
II. GABA _C Antagonists	280
F. Modulation of GABA _C Receptors	283
I. Extracellular Modulation	283
II. Intracellular Modulation by Protein Kinases	284
G. Physiological Function of GABA _C Receptors	287
H. Terminology for GABA _C Receptors	290
I. Conclusions	290
References	291

GABA_B Receptors**CHAPTER 11****Structure of GABA_B Receptors**

B. BETTLER and K. KAUPMANN. With 2 Figures	299
A. Physiological Evidence for GABA _B Receptor Subtypes	299
B. Pharmacology, Structure and Distribution of Cloned GABA _B Receptors	300
I. Cloned GABA _B Receptors	300
II. Binding Pharmacology	302
III. Molecular Determinants of Ligand Binding	302
C. Functional Studies with Recombinant GABA _B Receptors	303
I. Individually Expressed BR1 and BR2 Receptors	303
II. Heteromeric BR1 + BR2 Receptors	305
D. Temporal and Spatial Distribution of Cloned GABA _B Receptors	306
E. Concluding Remarks and Future Directions	307
References	307

CHAPTER 12**Pharmacology of GABA_B Receptors**

N.G. BOWERY	311
A. Introduction	311
B. Physiological Role	312
C. GABA _B Receptor Distribution and Localization in CNS	313
D. GABA _B Receptor Coupling to Adenylate Cyclase	314
E. Ca ⁺⁺ and K ⁺ Channel Coupling to GABA _B Sites	315
F. Pharmacological Effects – GABA _B Receptor Agonists	316
G. Pharmacological Effects – GABA _B Receptor Antagonists	319
H. Subtypes of Receptor	321
References	321

CHAPTER 13**GABA_B Receptor Signaling Pathways**

S.J. ENNA. With 3 Figures	329
A. Introduction	329
B. Second Messenger Production	330
I. Overview	330
II. cAMP	330
III. Gene Transcription	334
C. Calcium Channels	336
D. Potassium Channels	337

E. Conclusion	338
References	339

GABA Transporters

CHAPTER 14

Structure and Function of GABA Transporters

B.I. KANNER	345
A. Introduction	345
B. Stoichiometry	346
C. Reconstitution and Purification	346
D. Biochemical Characterisation of the GABA Transporter	347
E. A New Superfamily of Na-Dependent Neurotransmitter Transporters	348
F. Topology	348
G. Structure-Function Relationships	349
H. Conclusions	351
References	352

CHAPTER 15

Pharmacology of GABA Transporters

J.E. CLARK and W.A. CLARK. With 4 Figures	355
A. Introduction	355
B. Physiological Relevance of GABA Transporters	356
C. 'Neuronal'- and 'Glial'-Specific GABA Transport Inhibitors	357
D. GABA Transporter Heterogeneity	359
E. Lipophilic GABA Transport Inhibitors	361
I. THPO	361
II. Prodrugs of Nipecotic Acid, Hydroxynipecotic Acid, and Isoguvacine	361
III. Nipecotic Acid and Guvacine Derivatives	362
F. Specific GABA Transport Inhibitors	364
I. Compounds Selective for GAT-1	364
II. Compounds Selective for GAT-2, GAT-3, and BGT-1	365
G. GABA Uptake Inhibitors as Experimental Tools	366
I. GABA Transport Inhibition and Sleep	366
II. Depolarizing Effects of GABA and Inhibition of GABA Uptake	367
H. Conclusion	367
References	368

Section III: Pharmacology of the Glycine System**CHAPTER 16****Structures, Diversity and Pharmacology of Glycine Receptors and Transporters**

H. BETZ, R.J. HARVEY, and P. SCHLOSS. With 3 Figures	375
A. Introduction	375
I. The Neurotransmitter Glycine	375
B. Structure and Diversity of Glycine Transporters	376
I. Structure of Plasma Membrane Glycine Transporters	376
II. Diversity and Regulation of Plasma Membrane Glycine Transporters	378
III. Distribution of Plasma Membrane Glycine Transporters and Possible Physiological Function.	380
IV. The Vesicular Glycine/GABA Transporter	381
C. Structure and Diversity of Glycine Receptor Channels	382
I. GlyRs are Ligand-Gated Ion Channels of the nAChR Superfamily	382
II. Glycine Receptor Isoforms	384
III. Ligand-Binding Determinants	385
IV. Ion Channel Function	387
V. The Peripheral Membrane Protein Gephyrin	387
VI. Pharmacology of GlyRs	389
1. Antagonism of GlyR Function by Strychnine	389
2. Amino Acids and Piperidine Carboxylic Acid Compounds	390
3. Picrotoxinin, Cyanotriphenylborate, and Quinolinic Acid Derivatives	390
4. Potentiation of GlyR Function by Anesthetics, Alcohol, and Zn^{2+}	391
D. Concluding Remarks	393
References	393
Subject Index	403