

CNS Neuroprotection

Contributors

M.F. Beal, K.J. Becker, A. Blesch, D.W. Choi, T.M. Dawson,
V.L. Dawson, H.J. Federoff, G.Z. Feuerstein, A.C. Foster,
S. Gandy, M.P. Goldberg, J.M. Hallenbeck, M.W. Halterman,
M. Jackson, G.A. Kerchner, A.H. Kim, W. Koroshetz,
M.P. Mattson, L.P. Miller, J.W. Phillis, R.M. Poole, H.D. Rosas,
J.D. Rothstein, M. Sasaki, C.P. Taylor, M.H. Tuszynski,
K.K.W. Wang, X. Wang, J.B. Wiesner

Editors

Frank W. Marcoux and Dennis W. Choi



Springer

Contents

Section I: Mechanic Approaches to CNS Neuroprotection

CHAPTER 1

Blocking Excitotoxicity

A.H. KIM, G.A. KERCHNER, and D.W. CHOI	3
A. Introduction	3
B. Contributions to Disease	3
C. Excitotoxicity in Brief	4
D. Extending Excitotoxicity to Glia	6
E. Points of Intervention	7
I. Reducing Extracellular Glutamate	7
1. Circuit Activity and Glutamate Release	7
a) Hypothermia	8
b) Increasing GABAergic Tone	8
c) Opening K ⁺ Channels	9
d) Modulating Adenosine Receptors	9
e) Blocking Voltage-Gated Na ⁺ Channels	10
f) Blocking Voltage-Gated Ca ²⁺ Channels	11
2. Glutamate Transport	12
II. Manipulating Glutamate Receptors	12
1. NMDA Antagonists	12
2. AMPA/Kainate Antagonists	16
3. Metabotropic Glutamate Receptors	17
III. Blocking Downstream Mediators	18
1. Downstream Effects of Cellular Ca ²⁺ Overload	18
2. Free Radical Formation	19
3. The Role of PARP	20
F. A Cautionary Note for Antiexcitotoxic Strategies: Enhanced Apoptosis?	21
References	22

CHAPTER 2

Limiting Apoptosis as a Strategy for CNS Neuroprotection

K.K.W. WANG. With 4 Figures	37
A. Definition of Necrosis and Apoptosis	37
B. Scheduled Apoptosis in the Development of the CNS	39
C. Unscheduled Apoptosis in Various Neurodegenerative Conditions	40
I. Criteria Used to Identify Neuronal Apoptosis	40
II. Various Neurodegenerative Disorders with Evidence of Apoptosis	40
D. Key Pathways and Components Relevant to Neuronal Apoptosis	42
I. Overview of Apoptosis-Linked Factors	42
II. Bcl-2/Bax Family	42
III. Mitochondria and Caspase-9 Mediated Pathway	43
IV. Death Receptor-Mediated Caspase-8/10 Pathway	44
V. TNF Receptor 1-Mediated p38 Kinase, JNK and NF- κ B Activation	45
VI. Akt-IP3 Kinase-Mediated Antiapoptosis Pathway for NGF and Other Survival Factors	48
VII. Effector Caspases	49
VIII. Participation of Other Proteases	51
IX. Reactive Oxygen Species	51
X. Neuronal-Specific Apoptosis Factors (cdk5, NAIP)	52
E. Comparison of the Potential of Neuronal Apoptosis Factors as Neuroprotective Drug Targets	53
References	54

CHAPTER 3

Reducing Neuroinflammation

K.J. BECKER and J.M. HALLENBECK	65
A. Introduction	65
B. The Central Nervous System Inflammatory Response	66
I. Initiation of the Inflammatory Response	66
II. Consequences of Leukocyte Activation	67
III. Cytokines in Brain Injury	69
1. Interleukin-1 β	69
2. Tumor Necrosis Factor α	71
3. Interleukin-6	72
4. Interleukin-8	73
IV. Nuclear Transcription Factor- κ B	73
V. Leukocyte Adhesion	74

VI. Temporal Profile of the Postischemic Inflammatory Response	76
1. Experimental Models	76
2. Clinical Data	77
VII. Endogenous Modulators of Inflammation	78
C. Ischemic Tolerance	79
D. Chronic Inflammatory Disease	80
E. Conclusions	81
References	81

CHAPTER 4

Mitochondrial Approaches to Neuroprotection

M.F. BEAL	95
A. Introduction	95
B. Approaches to Neuroprotection	96
I. Mitochondrial Oxidative Interactions	96
II. Mitochondrial Permeability Transition	97
III. Therapeutic Approaches for Neurodegenerative Disease	99
IV. Neuroprotective Effects of Coenzyme Q ₁₀	99
V. Neuroprotective Effects of Nicotinamide	100
VI. Neuroprotective Effects of Creatine	101
VII. Creatine and the MPT	102
VIII. Other Potential Neuroprotective Mechanisms of Creatine	102
IX. Creatine Uptake	103
X. Studies in Man	105
C. Conclusions	106
References	106

CHAPTER 5

Stabilizing Calcium Homeostasis

M.P. MATTSON. With 12 Figures	115
A. Introduction	115
B. Regulation of Calcium Homeostasis in Neurons	116
I. Plasma Membrane Systems	117
II. Endoplasmic Reticulum	118
III. Mitochondria	121
IV. Other Proteins Involved in Calcium Regulation	123
C. Factors That Destabilize Calcium Homeostasis	126
I. Oxidative Stress	126
II. Metabolic Impairment	130

III. Excitatory Imbalances	131
IV. Glucocorticoids	131
V. Apoptotic Mechanisms	132
D. Factors That Stabilize Calcium Homeostasis	135
I. Neurotrophic Factors	135
II. Cytokines	136
III. Inhibitory Neurotransmitters	138
IV. Antioxidants	138
V. Calcium-Binding Proteins	139
VI. Heat Shock Proteins	139
VII. Cytoskeletal Dynamics	139
E. Strategies to Preserve and Restore Neuronal Calcium Homeostasis	143
References	144

CHAPTER 6

Blocking Nitric Oxide Toxicity

M. SASAKI, T.M. DAWSON, and V.L. DAWSON	155
A. Introduction	155
B. Nitric Oxide Synthase	155
I. Neuronal Nitric Oxide Synthase	156
II. Endothelial Nitric Oxide Synthase	156
III. Immunologic Nitric Oxide Synthase	157
C. Inhibitors of Nitric Oxide Synthase	157
I. L-Arginine Site	158
1. Thiocitrullines	158
2. Nitro-Indazoles	158
3. Substituted Guanidines	160
4. Isothioureas	161
5. Imidazole	161
II. Tetrahydrobiopterin	161
III. Flavoprotein Inhibition	162
IV. NADPH Oxidase Inhibition	162
V. Calmodulin Inhibition	162
VI. Phosphorylation Sites	163
VII. Miscellaneous Inhibitors of NOS	163
D. Biochemical Regulation of NOS Catalytic Activity	164
E. Nitric Oxide and Neurologic Disease	164
I. Excitotoxicity and Experimental Stroke	164
II. Parkinson's Disease	165
III. HIV Dementia	165
IV. Multiple Sclerosis	166
F. Conclusions	166
References	167

Section II: Neuroprotective Agents**CHAPTER 7****Adenosine-Based Approaches to the Treatment of Neurodegenerative Disease**

A.C. FOSTER, L.P. MILLER, and J.B. WIESNER. With 1 Figure	177
A. Introduction	177
B. The Adenosine System in the Central Nervous System	178
I. Adenosine Receptor Subtypes	180
1. A ₁ Receptors	180
2. A ₃ Receptors	181
3. A _{2A} and A _{2B} Receptors	181
II. Adenosine Transporters	182
C. The Role of Adenosine in Central Nervous System Physiology	182
D. The Role of Adenosine in Central Nervous System Pathophysiology	185
E. Therapeutic Approaches to Adenosine-Based Neuroprotection in Cerebral Ischemia	187
I. Potential Therapeutic Mechanisms	187
II. Receptor-Based Approaches	187
1. A ₁ Receptor Agonists	187
2. A ₃ Receptor Agonists/Antagonists	189
3. A _{2A} Receptor Antagonists	189
III. Modulation of Endogenous Adenosine	189
1. Adenosine Transport Inhibitors	190
2. Adenosine Deaminase Inhibitors	191
3. Adenosine Kinase Inhibitors	192
4. Other Adenosine Modulators	193
5. A ₁ Receptor Modulators	193
F. Adenosine-Based Therapeutics in Parkinson's Disease	194
I. A _{2A} Antagonists	194
II. Adenosine Modulators	196
G. Adenosine-Based Therapeutics in Epilepsy	197
I. A ₁ Receptor Agonists	197
II. Adenosine Modulators	198
H. Conclusions	199
Abbreviations	199
References	200

CHAPTER 8

Sodium and Calcium Channel Blockers

C.P. TAYLOR. With 3 Figures	209
A. Introduction	209
B. Structure and Function of Voltage-Gated Cation Channels	210
I. Molecular Biology and Protein Structure	210
1. Basic Structure of Channel Proteins	210
2. Auxiliary Ion Channel Subunit Proteins	215
II. Activation and Inactivation	216
1. Activation Gating	216
2. Inactivation Processes	216
III. Binding Sites for Blockers and Modulators	217
1. Tetrodotoxin and Conopeptides	217
2. Voltage-Dependent Blockers	217
C. Peptides as Specific Ca^{2+} Channel Probes	228
D. Mechanisms of Ischemic Neurotransmitter (Glutamate) Release	229
I. Ca^{2+} -Dependent Release	229
II. Ca^{2+} -Independent Release	230
E. Neuroprotection with Na^+ Channel Blockers	231
F. Neuroprotection with Small Molecule Ca^{2+} Channel Blockers	231
G. Neuroprotection with Conopeptides	232
H. Mixed Na^+ and Ca^{2+} Channel Blockers	233
I. Conclusions	233
References	234

CHAPTER 9

Neuroprotection by Free Radical Scavengers and Other Antioxidants

J.W. PHILLIS. With 8 Figures	245
A. Introduction	245
B. Free Radical Formation in the CNS	246
I. Reactive Oxygen Species	246
1. Mitochondrial Activity	246
2. Excitotoxic Amino Acids	246
3. Arachidonic Acid Metabolism	247
4. Purine Catabolism	247
5. Neutrophils	248
6. Auto-oxidation of Catecholamines	249
II. Reactive Nitrogen Species	249
C. Oxidative Stress in the CNS	250
D. Evidence of Free Radical Generation in the CNS	250

E. Antioxidant Defenses	251
F. Cerebroprotective Effects of Administered Antioxidants	254
I. Free Radical Scavengers	254
1. Spin-Trapping Agents	254
2. Mannitol, Dimethylthiourea and Dimethylsulfoxide	258
3. α -Lipoic Acid	259
4. α -Tocopherol	259
5. Superoxide Dismutase and Catalase	260
II. Inhibition of ROS/RNS Formation	261
1. Xanthine Oxidase Inhibitors	261
2. Inhibition of Phospholipases and Arachidonic Acid Metabolism	262
3. Inhibitors of Nitric Oxide Synthases	263
III. Chelation of Metal Ions	264
G. Oxidative Injury and Age-Related Neurodegeneration	265
H. Oxidative Stress and Neurogenerative Diseases	266
I. Amyotrophic Lateral Sclerosis	266
II. Alzheimer's Disease	266
III. Parkinson's Disease	267
IV. Huntington's Disease	268
I. Conclusions	268
Abbreviations	269
References	269

CHAPTER 10

Chemokines and Chemokine Receptors in the Central Nervous System: New Opportunities for Novel Therapeutics in Brain Ischemia and Trauma

G.Z. FEUERSTEIN and X. WANG. With 6 Figures	281
A. Introduction	281
I. The Chemokine Family of Polypeptides and Their Receptors	281
B. Chemokine and the Central Nervous System	285
C. Chemokine Expression in Brain Trauma	286
D. Chemokines and Cerebral Ischemia	287
I. Cytokine-Induced Neutrophil Chemoattractant	287
II. Monocyte Chemoattractant Protein 1	287
III. Monocyte Chemottractant Protein 3	289
IV. Interferon- γ -Inducible Protein 10	289
E. Interleukin-8 in Human Brain Injury	291
F. Chemokines and Neuro-Acquired Immune Deficiency Syndrome	293
G. Chemokines in Neurodegenerative Disorders	293
H. Summary and Conclusion	294
References	295

Section III: CNS Delivery of Neuroprotective Therapies

CHAPTER 11

Ex Vivo Gene Therapy in the Central Nervous System

A. BLESCH and M.H. TUSZYNSKI. With 5 Figures	301
A. Introduction	301
B. Gene Therapy Versus Conventional Drug Delivery	302
C. Practical Considerations	302
I. Cell Types Suitable for Gene Transfer and Grafting to the CNS	302
II. Methods of Ex Vivo Gene Transfer	304
III. Transplantation of Genetically Modified Cells to In Vivo Models of CNS Disease	307
D. Experimental Therapies in Animal Models of Neurodegenerative Diseases	307
I. Alzheimer's Disease	308
1. Nerve Growth Factor	309
2. Biochemical Modulation of Acetylcholine Levels	312
II. Parkinson's Disease	312
1. Neuroprotective Strategies	313
2. Biochemical Modulation of Dopamine Levels	314
III. Huntington's Disease	314
IV. Amyotrophic Lateral Sclerosis	317
E. Experimental Therapies in Animal Models of Spinal Cord Injury	319
F. Experimental Therapies of Brain Tumors	323
G. Future Perspectives	324
References	324

CHAPTER 12

**Developing Gene-Based Neuroprotection Strategies Using Herpes
Amplicon Vectors**

M.W. HALTERMAN and H.J. FEDEROFF. With 3 Figures	335
A. Introduction	335
B. Central Nervous System Ischemia Induces Distinct Patterns of Neuron Loss	336
C. A Cell-Autonomous Program Activates the Delayed Form of Neuronal Death	337
I. Mitochondria Can Sense and Activate Delayed Death	338
D. Herpes Virus-Mediated Gene Delivery	340
I. The Herpes Amplicon Vector System	340

II. Application of Amplicon Vectors in Neuroscience Research 341

E. Developing Neuroprotective Viral Vector Strategies 342

 I. Targeting the Late Stage of Delayed Death: IL-1 β and Caspase Activity 342

 II. Targeting the Intermediate Stage of Delayed Death: *bcl-2* 344

 1. Viral Delivery of *bcl-2* Protects Ischemic Neurons 345

F. Using Viral Vectors to Regulate Early Ischemic Transcriptional Responses 347

 I. HIF-1 α and p53 Regulate Ischemic Gene Expression 348

 II. Disruption of HIF-1 α Signaling Protects Against Ischemia-Induced Delayed Neuronal Death 349

G. Conclusions 351

References 351

Section IV: Disease Targetily of Newoportective Therapies

CHAPTER 13

Stroke

M.P. GOLDBERG 361

A. Introduction 361

 I. Cerebrovascular Disorders Defined 361

 II. Scope of the Problem 363

 III. Rationale for Development of Neuroprotective Agents 364

B. Clinical Trials of Neuroprotective Agents 365

 I. Progress in Clinical Trials and Trial Designs 365

 II. Glutamate Antagonists 365

 1. NMDA Receptor Antagonists 368

 2. AMPA Receptor Antagonists 369

 III. Other Receptor Agents 370

 IV. Ion Channel Blockers 370

 V. Antioxidants and Lipid Peroxidation Inhibitors 372

 VI. Inhibitors of Inflammation or Leukocyte Activation 372

 VII. Agents with Other Mechanisms of Action 372

C. Issues Regarding Preclinical Stroke Research 373

D. Issues Regarding Clinical Stroke Research 375

 I. Drug Dosing 375

 II. Time of Drug Delivery 377

 III. Clinical Trial Design and Outcomes 378

 IV. Publication of Trial Results 380

D. Conclusions 381

References 381

CHAPTER 14

Traumatic Central Nervous System Injury

R.M. POOLE. With 1 Figure 387

A. Introduction 387

B. Clinical Trial Experience in Traumatic Brain Injury 387

 I. Adequate Characterization of Compounds in Preclinical Experiments 388

 II. Characterization of Compounds in Early Clinical Development 390

 III. Special Challenges of Trial Design and Conduct for TBI 393

 1. Short Enrollment Time Window 393

 2. Characterization and Stratification of the Study Population 394

 3. Standardization of Care 396

 4. Outcome Measures 397

C. Spinal Cord Injury Clinical Trials 403

D. Conclusions 404

References 404

CHAPTER 15

Neurohormonal Signalling Pathways and the Regulation of Alzheimer β -amyloid Metabolism

Integrating Basic and Clinical Observations for Developing Successful Strategies to Delay, Retard or Prevent Cerebral Amyloidosis in Alzheimer's Disease

S. GANDY. With 1 Figure 409

A. Alzheimer's Disease Is Associated with an Intracranial Amyloidosis 409

B. $A\beta$ Is a Catabolite of an Integral Precursor 410

C. Pathogenic APP Mutations Occur Within or Near the $A\beta$ Domain 413

D. Signal Transduction Regulates the Relative Utilization of APP Processing Pathways in Cultured Cell Lines, in Primary Neurons, and in Rodents In Vivo 414

E. Insights into Mechanism(s) of Regulated APP Processing 416

F. Therapeutic Manipulation of $A\beta$ Generation Via Ligand or Hormonal Manipulation 417

References 418

CHAPTER 16

Amyotrophic Lateral Sclerosis

M. JACKSON and J.D. ROTHSTEIN	423
A. Introduction	423
B. Pathological Mechanisms	424
I. Free Radicals and Oxidative Stress	424
II. Cytoskeletal Abnormalities	424
III. Autoimmune Factors	426
IV. Excitotoxicity	426
C. Mechanism of Motor Neuron Degeneration	428
D. Clinical Trials	429
I. Neurotrophic Factors	430
II. Antioxidant Drugs	430
III. Antiexcitotoxic Agents	431
E. Development of Preclinical Screening Models	432
F. Future Therapies	436
G. Conclusions	438
References	439

CHAPTER 17

Therapeutics in Huntington's Disease

H.D. ROSAS and W. KOROSHETZ. With 5 Figures	447
A. Background	447
B. The Pathology of Huntington's Disease	448
C. Molecular Basis of Huntington's Disease	451
I. Wild-Type Huntingtin	451
II. Huntingtin with Expanded Polyglutamine Repeat	452
1. Huntingtin and Altered Gene Transcription	454
2. Pathologic Intracellular Inclusions of Huntingtin	455
III. Reversibility of Molecular Pathology	456
IV. Apoptosis	456
D. Genetic Animal Models of HD	457
E. Potential Therapeutic Targets	459
I. Glutamate-Mediated Excitotoxicity in HD	460
II. NMDA Receptor	461
III. Selective Neuronal Loss	463
IV. Selective Vulnerability: Toxins	464
F. Potential Therapeutics Agents	464
I. Glutamate Release Inhibitors	465
II. NMDA Channel Blockers	465
III. Metabotropic Receptor Modulators	466
IV. Free Radical Inhibitors	466
V. Nitric Oxide Synthase Inhibitors	466

G. Energy Metabolism and Its Relationship to Neurodegeneration 467

 I. Mitochondrial Permeability Transition Pore 469

H. Neuroprotective Strategies 470

 I. Antioxidants 471

 II. Free Radical Spin Traps 471

 III. Energy Boosters 472

 IV. Targets Against the Mitochondrial Permeability Transition Pore 473

 V. Neurotrophic Factors 473

I. Future Potential Therapeutics 475

 I. Caspase Inhibitors 475

 II. Bcl-2 476

 III. Gene Transcription and Histone Deacetylation Inhibitors 477

 IV. Neural Transplantation 477

J. Challenges for Clinical Research 477

K. Conclusions 480

References 480

Subject Index 493