

Neuroprotection

Part I: Drugs & Markets

By

Prof. K. K. Jain
MD, FRACS, FFPM
Jain PharmaBiotech
Basel, Switzerland

September 2017

A Jain PharmaBiotech Report

A U T H O R ' S B I O G R A P H Y

Professor K. K. Jain is a neurologist/neurosurgeon by training with specialist qualifications. He received graduate training in both Europe and USA and has held academic positions in several countries. He has been involved in biotechnology/pharmaceutical industry since 1989 and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of UK since 2000. After his retirement from neurosurgery, he is a consultant at Jain PharmaBiotech in Basel, Switzerland.

Prof. Jain's 470 publications include 28 books (5 as editor + 23 as author) and 50 special reports, which have covered important areas in biotechnology, gene therapy and biopharmaceuticals. As associate editor and contributing author of MedLink Neurology (San Diego, California), he is responsible for writing and yearly updating of 160 articles for continuing education of neurologists in an electronic encyclopedia of neurology. He has also written the Textbook of Gene Therapy, which was translated into Chinese, and a book on gene therapy companies published in 2000 by John Wiley & Sons. Prof. Jain has edited "Drug Delivery Systems" (Humana/Springer, 2008; 2nd ed 2014) and "Drug Delivery to the Central Nervous System", (Springer/Humana 2010). His recent books include "Handbook of Nanomedicine" (Springer/Humana 2008, Chinese edition by Peking University Press, 2011; 3rd ed Springer 2017), "Drug-induced Neurological Disorders, 3rd ed" (Hogrefe 2011), "Textbook of Personalized Medicine" (Springer 2009; Japanese ed 2012; 2nd ed Springer, 2015), "Handbook of Biomarkers" (Springer 2010; Chinese edition, Chemical Industry Press 2016, 2nd ed Springer 2017), "Handbook of Neuroprotection" (Springer 2011), and "Applications of Biotechnology in Neurology" (Springer 2013). He has also edited "Applied Neurogenomics" (Springer 2015).

Prof. Jain has been involved in various neuroprotective strategies during his active neurosurgical career including use of hypothermia, hyperbaric oxygen and induced coma. He has a personal experience of methods of neuroprotection used in the care of patients with stroke and CNS trauma as well as during neurosurgical operations.

**September 2017 (first edition published in April 2000)
Copyright © 2017 by:**

**Jain PharmaBiotech
Bläsiring 7
CH-4057 Basel
Switzerland**

**Tel & Fax: +4161-6924461
Email: info@pharmabiotech.ch
Web site: http://pharmabiotech.ch/**

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, or otherwise without the prior written permission of the Publisher. This report may not be lent, resold or otherwise traded in any manner without the consent of the Publisher. While all reasonable steps have been taken to ensure the accuracy of the information presented, the Publisher cannot accept responsibility for inadvertent errors or omissions.

TABLE OF CONTENTS

0. Executive Summary	27
1. Introduction	31
Definitions	31
Historical development of neuroprotection	31
Neurophysiological basis of neuroprotection	32
Astrocytic glycogen-derived lactate as fuel for the brain.....	32
Gene expression in the human brain	32
Role of astrocytes in neuroprotection.....	33
Role of glymphatic system in neuroprotection.....	33
Role of sleep in neuroprotection.....	34
Role of cerebral metabolism in neuroprotection	34
Role of circadian genes in neuroprotection	34
Role of blood-brain barrier in neuroprotection.....	35
<i>Role of the gut microbiota in development of integrity of the BBB</i>	<i>35</i>
Intrinsic neuroprotective factors	35
Neuroprotective gene expression	37
<i>Upregulation of GADD34.....</i>	<i>37</i>
<i>Induction of NR4A proteins by CREB in neurons.....</i>	<i>37</i>
<i>Elevation PGC-1α for neuroprotection in PD.....</i>	<i>37</i>
Neurotrophic factors.....	38
Intrinsic nonenzymatic antioxidants	38
Activation of transcription factor Nrf2	38
Intrinsic neuroprotective proteins.....	39
<i>αB-crystallin.....</i>	<i>39</i>
<i>Excitatory amino acid transporters.....</i>	<i>39</i>
<i>Extracellular serine protease thrombin.....</i>	<i>39</i>
<i>Galanin.....</i>	<i>39</i>
<i>Neuroglobin</i>	<i>40</i>
<i>Nuclear factor I-A</i>	<i>40</i>
<i>Prion protein</i>	<i>41</i>
<i>Rai adaptor protein</i>	<i>41</i>
Stem cell factor	41
Role of the immune system in neuroprotection	41
Induction of DNA repair enzymes for neuroprotection.....	42
Microtubule-based neuroprotective response to axonal injury	43
Pathomechanisms of CNS injury as basis for neuroprotection	43
Biomarkers of neurological disorders and neuroprotection.....	44
CNS biomarker identification using proteomics	44
Brain imaging for detection of biomarkers.....	44
Role of neuroprotection in various neurological disorders	45
Neuroprotection and neuroregeneration.....	46
Acute versus chronic neuroprotection	46
Discovery and evaluation of neuroprotective agents	46
Neuroprotective drug discovery	46
Discovery of CNS drugs that penetrate the blood-brain barrier	47
In vitro assays for the evaluation of neuroprotective agents.....	47
Oxidative injury model to test neuroprotective drugs.....	48
Apoptosis model for designing neuroprotective drugs	48
Transgenic mouse models of neurological disorders.....	49
Evaluating effects of neuroprotective drugs on living brain slices.....	49
Role of brain imaging in neuroprotective drug discovery and development	49
<i>Positron emission tomography.....</i>	<i>50</i>
<i>Role of single photon emission computed tomography.....</i>	<i>50</i>
<i>Functional CT scanning to evaluate cerebrovascular protection</i>	<i>50</i>
<i>Magnetic resonance imaging for the evaluation of neuroprotectives.....</i>	<i>51</i>
Application of nanotechnology to neuroprotection	51
<i>Nanoparticles as neuroprotective antioxidants.....</i>	<i>52</i>
<i>Cadmium telluride nanoparticles prevent Aβ fibril formation</i>	<i>53</i>
Evaluation criteria for potential neuroprotective agents.....	53
2. Neuroprotective Agents	55
Classification of neuroprotective agents	55
α2 adrenoreceptor agonists	59
Dexmedetomidine.....	59
Activated protein C	60
Activity-dependent neuroprotective protein	60

Davunetide	60
Adenosine analogs.....	60
Propentofylline	61
Antidepressants.....	61
Antidepressant-induced neurogenesis.....	61
Neurogenesis induced by electroconvulsive therapy	62
Neuroprotective effect of selective serotonin reuptake inhibitors	62
Antiepileptic drugs as neuroprotectives.....	64
BIS-001.....	65
Levetiracetam	65
Phenytoin	65
Valproic acid.....	66
Antiinflammatory agents	66
Aspirin.....	66
Interleukin-1 antagonists.....	67
COX-2 inhibitors	67
<i>Nimesulide</i>	67
Gold microparticles as anti-neuroinflammatory agents.....	68
Minocycline	68
Prostaglandin receptor antagonists.....	69
Anti-apoptosis agents.....	70
Activated protein C	70
Calpain inhibitors	70
Caspase inhibitors.....	71
DNA binding drugs	71
Lithium.....	71
Melatonin.....	72
Olesoxime.....	72
Omega-3 fatty acids.....	72
<i>Docosahexaenoic acid</i>	72
Poly(ADP-ribose) polymerase inhibitors	73
Prevention of apoptosis by binding of proNGF to sortilin.....	74
Antioxidants/free radical scavengers	74
Free radical generation	74
Natural defenses against oxidative stress.....	74
Effects of oxidative damage	75
<i>Oxidative damage and aging</i>	75
<i>Neuronal damage by free radicals</i>	76
<i>Oxidative damage and neurodegenerative disorders</i>	76
Measures to control oxidative stress.....	76
<i>Categories of therapeutic antioxidants</i>	76
<i>Alpha-phenyl-tert-butyl nitron</i>	77
<i>Coenzyme Q10</i>	77
<i>Dihydroergocryptine</i>	78
<i>Flavonoids</i>	78
<i>Mitochondria-targeted antioxidants</i>	79
<i>Neuroleptics as antioxidants</i>	79
<i>Nitrones</i>	79
<i>NRF2 for augmenting neuroprotection against oxidative stress</i>	79
Translation of antioxidant neuroprotection from preclinical to clinical.....	80
Carbon monoxide and heme oxygenase.....	80
Cell transplants.....	81
Cells secreting neuroprotective substances.....	81
Stem cells.....	81
Stem cell activation for neuroprotection/regeneration by glucocorticoids.....	81
Use of neural stem cells to construct the blood brain barrier.....	82
Cytokines.....	82
Erythropoietin	82
<i>Non-erythropoietic EPO variants and mimics</i>	83
Granulocyte colony-stimulating factor.....	84
Delta-opioid receptor agonists.....	84
Delta opioid peptide-induced hibernation for neuroprotection	85
FK960	85
Gene therapy	85
Glucagon-like peptide.....	86
Glatiramer acetate.....	87
Glutamate antagonists.....	87
Neuroprotection by scavenging blood glutamate	88
N-acylethanolamines for protection against glutamatergic excitotoxicity	88
Glutamate transporters.....	89
Glutamate transporter-mediated neuroprotective effect of drugs.....	89

Neuroprotection by targeting KAI subunit of kainate receptor	90
Glycine-proline-glutamate analogs	90
Hydrogen sulfide.....	90
Hibernation induced by hydrogen sulfide.....	91
NMDA receptor ion channel complex.....	91
NMDA receptor antagonists	92
<i>NMDA NR2B subunit receptor antagonists</i>	<i>92</i>
<i>Ifenprodil.....</i>	<i>93</i>
<i>Memantine as a neuroprotective agent</i>	<i>93</i>
<i>NAALADase inhibitors</i>	<i>93</i>
<i>Gacyclidine</i>	<i>93</i>
<i>N-alkylglycines</i>	<i>94</i>
AMPA receptor modulators	94
Metabotropic glutamate receptor modulators.....	94
Cannabinoids.....	95
Dexanabinol	95
Glutathione.....	96
Heat shock proteins	96
Histone deacetylase inhibitors for neuroprotection	97
Hormones	97
Estrogen and neuroprotection.....	97
<i>Neuroprotective effect of estrogen receptor ligands.....</i>	<i>98</i>
<i>Selective estrogen receptor modulators</i>	<i>98</i>
<i>Mitochondrial mechanisms of estrogen neuroprotection</i>	<i>99</i>
Insulin	99
Ion Channel modulators	100
Calcium channel blockers.....	100
<i>Ziconotide.....</i>	<i>100</i>
Na ⁺ channel blockers.....	101
Neuroprotective potassium channel inhibitors.....	101
Kynurenine inhibitors	101
Leukocyte adhesion inhibitors	102
Modafinil.....	102
Neural regeneration protein	103
Neurite outgrowth-promoting prostaglandin compounds	103
Neuroimmunophilins.....	104
Cyclosporin-A	104
FK506	104
Rapamycin	105
Neurotrophic factors.....	105
Activity-dependent neurotrophic factor	105
Bone morphogenetic proteins	106
Brain-derived neurotrophic factor.....	106
Ciliary neurotrophic factor.....	106
Fibroblast growth factors	107
Glial cell line-derived neurotrophic factor	107
Insulin-like growth factor.....	108
Nerve growth factor	108
Neurotrophins	109
Osteogenic protein-1	110
Pigment epithelium-derived factor.....	110
Transforming growth factor-β1	110
Vascular endothelial growth factor	110
Neurotrophic factor-related neuroprotective agents	110
<i>Amitriptyline as a TrkA and TrkB receptor agonist</i>	<i>111</i>
<i>Colivelin.....</i>	<i>111</i>
<i>Gambogic amide.....</i>	<i>111</i>
<i>Inosine</i>	<i>111</i>
<i>Meteorin</i>	<i>112</i>
<i>Oxygen-regulated protein 150 kD</i>	<i>112</i>
<i>Prosaptide.....</i>	<i>112</i>
<i>Siagoside.....</i>	<i>112</i>
<i>Small molecule activators of the Trk receptors.....</i>	<i>113</i>
Nicotine and nicotinic receptor agonists	113
<i>Neuroprotective effect of galantamine mediated via α7nAChRs</i>	<i>114</i>
<i>Galantamine-induced Aβ clearance via α7nAChRs</i>	<i>114</i>
Nitric oxide-based neuroprotection	115
Nitric oxide synthase inhibitors	115
Nitric oxide mimetics	115
Nitric oxide donating derivatives	116
Nootropics	116

<i>Piracetam</i>	117
Nutraceuticals and naturally-derived compounds	117
Cinnamon	117
Coffee	117
Creatine.....	118
Curcumin/curry	119
<i>Mechanism of neuroprotective effect of curcumin</i>	119
Flavonoids	119
Glyceryltriacetate.....	119
Green tea	119
Herbal preparations.....	120
<i>Flavonoid wogonin</i>	120
<i>Ginseng</i>	120
Nicotinamide	121
Punicalagin from pomegranate	121
Resveratrol	121
Osmotic diuretics	122
Mannitol	122
Osteopontin	122
Oxygen therapeutics	123
Oxygen carriers	123
Hemoglobin-based oxygen carriers.....	123
Perfluorocarbons as oxygen carriers	124
Hyperbaric oxygen therapy	125
P7C3 compounds	125
Peptides	126
C3-derived peptide for neuroprotection and neuroregeneration	126
Corticotropin-releasing hormone.....	126
Thyrotropin-releasing hormone.....	126
Vasoactive intestinal peptide	127
Pharmacological preconditioning	127
PPARs as drug targets for neuroprotection	128
Proteins	128
Amyloid precursor protein	128
Protein kinase C activators.....	128
Riluzole	129
Role of RNA interference in neuroprotection	129
Role of miRNA in neuroprotection.....	129
Sigma receptor agonists as neuroprotective agents	130
SIRT group of proteins	130
Statins	131
Steroids	132
Dehydroepiandrosterone.....	132
HF0220	132
Sulforaphane	133
Tauroursodeoxycholic acid	133
Tetanus toxin as a neuroprotective agent	133
Thrombolytic agents as neuroprotective agents	134
Uncoupling protein 2	134
Vaccines as neuroprotectives	134
Vitamins as neuroprotective agents	135
Vitamin B12	135
Vitamin D	135
Non-pharmacological approaches to neuroprotection	136
Caloric restriction.....	136
Cerebral exercise	136
<i>Bilingualism for prevention of decline of mental function</i>	136
Electrical fields for improvement of cerebral function in neurodegeneration	137
Environmental enrichment	137
Hypothermia	137
<i>Limitations of hypothermia</i>	138
<i>Hypothermic neuroprotection in hypoxia-ischemia</i>	138
Ketogenic diet	139
Mediterranean diet.....	139
Nonpharmacological preconditioning for neuroprotection.....	139
Physical exercise.....	140
Suspended animation and neuroprotection	141
Transcranial magnetic stimulation	141
3. Neuroprotection in Cerebrovascular Disease	143
Introduction	143

Pathophysiology of cerebral ischemia.....	144
Calcium overload	144
Ion channel dysfunction in stroke.....	145
Role of oxygen free radicals in cerebral ischemia	145
Role of nitric oxide in cerebral ischemia	145
Glutamate as a biomarker of stroke	145
Cerebral edema in stroke.....	146
Gene expression in response to cerebral ischemia.....	146
Induction of heat shock proteins in stroke.....	146
Role of cytokines and adhesion molecules in stroke.....	147
<i>Tumor necrosis factor-α</i>	147
<i>Interleukin-1 and IL-6</i>	147
<i>Adhesion molecules</i>	147
DNA damage and repair in cerebral ischemia.....	147
Role of neurotrophic factors in stroke	148
<i>Problems requiring investigation of the role of NTFs in stroke</i>	148
Role of Poly(ADP-ribose) polymerase (PARP) gene	149
Role of protease-activated receptor 1	149
Reperfusion injury after cerebral ischemia	149
Neuroprotection according to zones in cerebral infarction.....	149
Zone of ischemic infarction.....	149
Penumbra	150
Current management of stroke	151
Neuroprotection in stenosis of intracranial arteries.....	151
Neuroprotection in stroke with intracerebral hemorrhage	151
Neuroprotection in cavernous cerebrovascular malformations.....	152
Neuroprotective strategies for ischemic stroke in patients with dementia	152
Neuroprotection in transient ischemic attacks.....	153
Secondary prevention of stroke	153
Neuroprotective therapies for stroke.....	153
Pharmacologic neuroprotective agents for stroke.....	154
α B-crystallin as a neuroprotectant in stroke	154
Acid-sensing ion channel blockers	155
AMPA receptor antagonists as neuroprotectives for stroke.....	155
<i>Zonampanel</i>	155
Antiapoptotic neuroprotectives	155
<i>NIM811</i>	155
<i>Creatine as neuroprotective in stroke</i>	156
<i>Lithium as a neuroprotective in stroke</i>	156
<i>TUDCA as a neuroprotective in stroke</i>	156
Antiepileptic drugs as neuroprotectives in stroke.....	157
<i>Tiagabine</i>	157
<i>Topiramate</i>	157
<i>Zonisamide</i>	157
Anti-HMGB1 monoclonal antibody	157
Antioxidant approaches	158
<i>Carnosine as a neuroprotective in stroke</i>	158
<i>Dehydroascorbic acid</i>	158
<i>Tocotrienols</i>	159
<i>Uric acid</i>	160
Antiglutamate compounds.....	160
<i>MRZ 2/576</i>	160
<i>L-Phenylalanine</i>	160
Arimocloamol for stroke	160
Cardiac glycosides as neuroprotectives in stroke.....	161
Clenbuterol	161
Coagulation inhibitors as neuroprotectives	161
<i>Heparin and enoxaparin</i>	161
<i>Warfarin vs dabigatran</i>	162
<i>Apixaban</i>	162
Cox-2 inhibitors for ischemic stroke.....	162
Curcumin as a neuroprotectant in stroke.....	162
Docosahexaenoic acid for ischemic stroke	163
Ephrin-A5 blockers.....	163
Estrogen for stroke	163
Extendin-4	165
Flavones for neuroprotection in stroke.....	165
<i>Epicatechin</i>	165
<i>Isorhamnetin</i>	165
Granulocyte-macrophage colony-stimulating factor for cerebral ischemia.....	166
Hamartin induction by cerebral ischemia as a basis for neuroprotection	166

Histone deacetylase inhibitors for neuroprotection in stroke	166
Histamine H ₂ -receptor modulation.....	167
Inosine for stroke	167
Insulin-like growth factor-I.....	167
Intravenous immunoglobulin as neuroprotective in stroke.....	167
Ischemic preconditioning for neuroprotection in stroke	168
Ketone bodies for neuroprotection in stroke	169
Magnesium	169
Mineralocorticoid receptor blockade for neuroprotection.....	169
miR-223 and neuroprotection in stroke.....	169
Multifunctional neuroprotective agents.....	170
NA-1 as neuroprotective against ischemic stroke	170
Nasal delivery of neuroprotective agents in stroke	170
Neuroserpin as a neuroprotective in stroke	170
N-2-mercaptopropionyl glycine	171
NeuroAiD	171
Neurotrophic factors as neuroprotectives for stroke.....	172
<i>Brain-derived neurotrophic factor</i>	172
<i>Fibroblast growth factor</i>	172
<i>G-CSF</i>	172
<i>Glial cell line-derived neurotrophic factor</i>	173
<i>Insulin-like growth factor-1</i>	173
<i>Neuregulin-1</i>	173
NO-based strategies for neuroprotection in cerebral ischemia	173
Omega-3 fatty acids for neuroprotection after cerebral ischemia-hypoxia.....	174
Pannexin channel blockers for neuroprotection in stroke	174
Perlecan domain V	175
Peroxisome proliferator-activated receptor- γ agonists	175
PGE ₂ EP2 receptor activation	175
Pioglitazone for reduction of stroke risk	175
Progesterone.....	176
Propofol as neuroprotective in stroke.....	176
Proteoglycan-degrading enzymes.....	176
Proteasome inhibitors.....	177
Statins for prevention and neuroprotection in stroke	177
Sildenafil	178
Src receptor blockade.....	178
Stroke vaccine.....	178
SUN N4057	178
Thrombosis inhibitors	179
<i>Aspirin</i>	179
<i>Clopidogrel</i>	179
<i>Dipyridamole</i>	179
<i>Ticagrelor</i>	180
Vitamin E for neuroprotection in stroke.....	180
Neuroprotection in ischemia-reperfusion injury	181
Aminoguanidine.....	181
Dexmedetomidine	181
Methylene blue for neuroprotection in ischemia-reperfusion injury	181
Miscellaneous agents for neuroprotection in reperfusion injury.....	182
Neuroprotection by treatment of cerebrovascular malformations.....	182
Cerebral cavernous malformations	182
Prevention of hemorrhage following ischemic stroke	182
Non-pharmacological neuroprotective therapies for stroke	183
Hypothermia for neuroprotection in acute stroke.....	183
Hyperbaric oxygen therapy for neuroprotection in acute stroke.....	183
Hypothermia combination with other neuroprotective strategies	184
Infrared laser therapy for ischemic stroke	185
Preconditioning for neuroprotection against cerebral ischemia	185
Neurosurgical procedures for stroke.....	186
Neurosurgical procedures for neuroprotection in acute stroke	186
Neurosurgical procedures for chronic cerebral ischemia	188
Neurostimulation of sphenopalatine ganglion.....	188
Stent versus surgery for asymptomatic carotid stenosis.....	188
Neurorehabilitation in relation to neuroprotection in stroke.....	189
Protective effect of physical activity on stroke in the elderly	189
Biological therapies for stroke	189
Cell therapy for stroke	189
<i>Stem cell transplant for stroke</i>	189
<i>Immortalized cell grafts for stroke</i>	190
<i>Stimulation of intrinsic stem cells for repair of brain in stroke</i>	190

Gene therapy for neuroprotection in cerebrovascular disease	191
Regulation of microRNAs for neuroprotection in cerebral ischemia	193
RNAi-based therapy for neuroprotection in stroke	193
Vaccines for neuroprotection in stroke	193
Neuroprotective therapies for cerebral ischemia: clinical trials	193
Albumin	194
Free radical scavengers	195
DP-b99	196
Mildronate.....	196
Minocycline for neuroprotection in stroke	197
Perindopril	197
Failed clinical trials of neuroprotection in stroke.....	197
<i>Ancrod</i>	199
<i>Aptiganel</i>	199
<i>Cerovive</i>	199
<i>Citicoline</i>	200
<i>Desmoteplase</i>	201
<i>Erythropoietin as a neuroprotective in stroke</i>	202
<i>SPD 502</i>	202
<i>Tirilazad mesylate</i>	203
<i>Selfotel</i>	203
<i>Lubeluzole</i>	203
<i>Nalmefene</i>	203
<i>Gavestinel</i>	204
<i>Nimodipine</i>	204
<i>Sipatrigine</i>	204
<i>Causes of failure of stroke trials</i>	204
Measures for prevention of failures in stroke trials	206
Design of acute stroke trial to facilitate drug approval	207
The ideal neuroprotective agent for stroke	208
Future of neuroprotection in stroke	208

4. Neuroprotection in Traumatic Brain Injury	211
Introduction	211
Cerebral hypoxia/ischemia as a complication of trauma.....	211
Epidemiology of TBI.....	211
TBI in the military	212
Pathophysiology of TBI.....	212
Immediate damage following TBI.....	213
Cerebral edema following TBI	213
Neurometabolic cascade after TBI	214
Delayed damage following TBI.....	214
Mechanism of axonal damage after TBI	215
Role of neuroinflammation in TBI	215
BBB damage after TBI	215
Molecular events following TBI.....	216
Chronic traumatic encephalopathy	216
Neurocognitive sequelae of TBI.....	218
Changes in neurotrophic factors following TBI	218
Changes in neurotransmitters following TBI.....	218
Proteomics of TBI	219
Genetic influences on outcome following TBI	219
Management of TBI	220
Management during acute phase of head injury	220
<i>Control of intracranial pressure and cerebral edema</i>	220
<i>Corticosteroids</i>	221
<i>Decompressive craniectomy</i>	222
Neuroprotection in TBI	222
Amantadine.....	223
Antioxidants	224
Barbiturates	224
β - and γ -secretase inhibitors	224
Beta blockers	224
Bradykinin B ₂ antagonists	225
Cell cycle inhibitors for TBI.....	225
COX-2 inhibitors for neuroprotection in TBI	225
Cyclosporin for neuroprotection in TBI	226
Dexanabol for TBI	226
Erythropoietin for neuroprotection in TBI	226
Gold implants for neuroprotection in focal TBI	227
Histone deacetylase inhibitors for neuroprotection in TBI	227

KN 38-7271	227
Levosimendan	227
Magnesium sulfate	228
Minocycline for TBI.....	228
Multipotential neuroprotective agents for TBI	228
Nutritional approaches to neuroprotection in TBI.....	228
<i>Branched chain amino acids to ameliorate cognitive impairment in TBI</i>	229
<i>Creatine for neuroprotection in TBI</i>	229
<i>Nicotinamide for neuroprotection in TBI</i>	230
<i>Omega 3 fatty acids as neuroprotectives in TBI</i>	230
Neurotrophic factors for TBI	230
Neurosteroids as neuroprotective agents for TBI	231
NMDA receptor antagonists	232
<i>Neuroprotection in TBI against glutamate-induced excitotoxicity</i>	232
<i>NP-1</i>	233
Nogo-A inhibitor	233
Oxygen carriers for TBI.....	233
Polyethylene glycol for neuroprotection in TBI	234
Propofol for neuroprotection in TBI.....	234
Rapamycin as neuroprotective in TBI.....	234
Simvastatin as neuroprotective in TBI	235
Thyrotropin-releasing hormone analogs	235
Traxoprodil	235
Biological approaches to neuroprotection in TBI	236
Antisense approaches to TBI	236
Cell therapy for TBI.....	236
Gene therapy for TBI.....	236
Vaccines for TBI.....	237
Non-pharmaceutical approaches to neuroprotection in TBI	237
Deep brain stimulation for TBI.....	237
Hyperbaric oxygen therapy for TBI.....	237
Hypothermia	238
Reduction of microglial migration after TBI.....	238
Vacuum for mechanical tissue resuscitation in TBI	238
Prophylactic neuroprotection against TBI.....	238
Role of helmets in protection against TBI	239
Role of physical exercise in protection against TBI	239
Neuroprotection against late sequelae of TBI	239
Antiepileptic drugs for prevention of seizures and neuroprotection	239
Neuroprotection during rehabilitation phase of TBI.....	240
Neuroregeneration following TBI.....	240
<i>Intrinsic factors that influence regeneration following TBI</i>	240
<i>Causes of lack of regeneration following TBI</i>	241
<i>Approaches to regeneration of the brain following TBI</i>	241
Clinical trials of neuroprotective agents in TBI	242
Ongoing clinical trials in TBI	242
Failed clinical trials in TBI.....	243
<i>Differences between clinical trials and studies in animal models of TBI</i>	244
<i>Subgroup analysis</i>	245
<i>Improving the clinical trial design</i>	245
<i>Clinical trials combining multiple treatment strategies</i>	245
<i>Shortening the trial time</i>	245
Conclusions and future prospects of neuroprotection in TBI.....	246
5. Neuroprotection in Spinal Cord Injury	247
Introduction	247
Pathophysiology of SCI.....	247
<i>Secondary mechanisms of SCI</i>	248
<i>Neurotrophic factor changes in SCI</i>	249
Management of SCI	250
Pharmacological neuroprotective agents for SCI	251
4-aminopyridine	251
Antibodies as neurite growth inhibitors in SCI.....	251
Antiexcitotoxic agents	251
<i>Gacyclidine</i>	251
<i>GM-1 ganglioside</i>	252
Bacterial enzyme chondroitinase ABC	252
Docosahexaenoic acid as neuroprotective in SCI	252
Erythropoietin as a neuroprotective in SCI	253
Free radical scavengers for neuroprotection in SCI	253
GYKI 52466	253

Immunosuppressants as neuroprotectants in SCI.....	253
Interleukin-10 for neuroprotection in SCI.....	254
Matrix metalloproteinase inhibitors for SCI.....	254
Methylprednisolone	254
Minocycline as neuroprotective in SCI.....	255
Modulation of macrophage responses for neuroprotection after SCI.....	255
Neurotrophic factors for neuroprotection after SCI	256
<i>Promotion of regeneration of neurons in SCI</i>	<i>256</i>
Rho pathway and Rho antagonists in SCI	257
Selenium as a neuroprotective for SCI.....	257
Sialidase for enhancing recovery after SCI	257
Targeting the inflammatory response for neuroprotection in SCI	258
Uric acid as neuroprotective in SCI.....	258
Non-pharmacological approaches to SCI	258
Hyperbaric oxygen therapy	258
Hypothermia for SCI	258
Cell therapy for SCI	259
Autoimmune T cells against CNS myelin-associated peptide	259
Fetal neural grafts for SCI.....	259
Olfactory-ensheathing cells for SCI	259
Oligodendrocyte precursor cells for treatment of SCI.....	260
Schwann cell transplants for SCI.....	260
Transplantation of glial cells for SCI	260
Stem cells for SCI	260
<i>Bone marrow stem cells for SCI.....</i>	<i>261</i>
<i>Embryonic stem cells for SCI.....</i>	<i>261</i>
<i>Transplantation of induced pluripotent stem cells in SCI</i>	<i>261</i>
<i>Transplantation of MSCs for SCI</i>	<i>262</i>
<i>Transplantation of NSCs for SCI.....</i>	<i>262</i>
<i>Transdifferentiation of stem cells into cholinergic neurons for SCI</i>	<i>263</i>
Gene therapy for SCI	263
Combined approaches to spinal cord injury	264
Discovery of new targets for neuroprotective therapies in SCI.....	265
Clinical trials in SCI.....	265

6. Neuroprotection in Neurodegenerative Disorders.....	267
Introduction	267
Pathomechanism of neurodegeneration	267
Aging and neurodegeneration.....	267
α-synuclein in neurodegeneration and neuroprotection	268
Dysregulation of cyclin-dependent kinase 5.....	268
Exosomes in CNS neurodegeneration and neuroregeneration.....	268
Genomics of neurodegenerative diseases	269
Impairment of neural transport in neurodegenerative disorders	269
Lack of neurotrophic factors	269
Neuroinflammation in neurodegenerative disorders.....	270
Neurodegeneration associated with protein misfolding	270
<i>Modulation of neurodegeneration by molecular chaperones</i>	<i>270</i>
<i>Intrabodies targeting protein misfolding in neurodegeneration.....</i>	<i>271</i>
<i>Targeting proteins aggregation to prevent amyloid formation</i>	<i>271</i>
<i>Tau and neurodegeneration.....</i>	<i>271</i>
Role of apoptosis in neurodegenerative disorders.....	272
Role of glia in neurodegeneration.....	272
Role of metals in neurodegeneration	272
Spread of neurodegeneration	273
TDP-43 proteinopathy and neurodegenerative diseases	273
Viral infections and neurodegeneration	273
<i>AIDS and the nervous system</i>	<i>273</i>
<i>Avian influenza as cause of neurodegeneration</i>	<i>274</i>
Neurodegenerative disorders with dementia	275
Dementia with Lewy bodies.....	275
Pick disease	276
<i>Progressive supranuclear palsy</i>	<i>276</i>
Genetic disorders with neurodegeneration	277
Batten disease.....	277
<i>Cell and gene therapies</i>	<i>277</i>
<i>Cerliponase alfa.....</i>	<i>278</i>
Familial dysautonomia	278
Friedrich ataxia.....	278
<i>Pathomechanism of FA</i>	<i>278</i>
<i>Neuroprotection in FA.....</i>	<i>279</i>

Leigh syndrome	279
Niemann-Pick type C disease	280
Spinal and bulbar muscular atrophy	280
<i>Spinal muscular atrophy</i>	281
Creutzfeldt-Jakob disease	282
Neuroprotection in Creutzfeldt-Jakob disease	282
<i>Pharmacological neuroprotectants against CJD</i>	283
<i>Innovative approaches to neuroprotection in CJD and future prospects</i>	284
Approaches to neuroprotection in neurodegenerative disorders	284
Glutamate-based therapies for neurodegenerative disorders	285
Histone deacetylase inhibitors for neurodegenerative disorders.....	285
Iron chelation for neuroprotection	285
Mitochondria permeability transition pore complex and neuroprotection.....	286
Modulation of proteostasis in neurodegenerative disorders	286

7. Neuroprotection in Parkinson Disease 287

Introduction	287
Epidemiology of Parkinson's disease	287
Pathophysiology of Parkinson's disease	287
Alteration of dopamine homeostasis	288
Apoptosis.....	288
Asynchronous neuronal activity	288
Disruption of iron homeostasis.....	289
Excitotoxicity.....	289
Genetic factors in PD	289
Oxidative stress.....	290
Role of neurotrophic factors	291
Role of misfolding proteins.....	291
Synaptic vesicle glycoprotein 2C disruption in PD	292
Neuroprotective strategies for PD based on pathomechanism	292
A genetic animal model of PD for testing neuroprotective strategies	293
Aldehyde dehydrogenase 1 protects nigrostriatal dopaminergic neurons	294
RNAi screening to identify neuroprotective genes in a PD model	294
Strategies to stop aggregation of α -synuclein	294
Management of Parkinson's disease	295
Limitation of conventionally administered dopamine therapy	296
Neuroprotective therapy in PD	297
Neuroprotective effect of currently used drugs for PD	297
Pramipexole	297
Rasagiline mesylate	298
Ropinirole	299
Rivastigmine for treatment of dementia and falls associated with PD	299
Selegiline.....	299
Non-pharmacological strategies for neuroprotection in PD	300
Deep brain stimulation for PD.....	300
Effect of exercise and environmental enrichment on PD	301
Low-calorie diet in PD.....	301
Development of neuroprotective therapies for PD	301
2B3-201 for targeted delivery of methylprednisolone.....	302
9-methyl- β -carboline.....	302
Adenosine A_{A2} receptor antagonists	302
Antiapoptotic strategies for PD	303
ATP13A2 activation	303
Augmenting CNS glucocerebrosidase activity	303
Calcium channel blockers for PD	304
Cell therapies for PD.....	304
<i>Stem cells for PD</i>	304
<i>Activation of endogenous stem cells and neural precursors</i>	304
Cogane.....	305
Creatine and minocycline	306
Conserved dopamine neurotrophic factor for PD.....	306
Doxycycline as a neuroprotectant in PD.....	306
Free radical scavengers for neuroprotection in Parkinson's disease.....	307
<i>Antioxidants</i>	307
<i>Diapocynin</i>	307
<i>Tea extracts as neuroprotectives</i>	307
Gene therapy for PD.....	307
<i>Implantation of genetically engineered cells</i>	308
<i>Gene therapy using GDNF and neurturin</i>	308
<i>Glutamic acid decarboxylase gene therapy</i>	309
<i>Parkin gene therapy</i>	309

<i>Concluding remarks about gene therapy for PD</i>	309
Heat shock protein 70	310
Liver X receptor β agonists.....	310
Melatonin as a neuroprotectant in PD	310
Nicotine as a neuroprotective in PD	311
Nilotinib for PD	311
Neuroprotective effect of leucine-rich repeat kinase-2 inhibitors	312
Neuroprotective effect of DJ-1 protein	312
Neurotrophic factors.....	312
<i>Basic fibroblast growth factor for PD</i>	312
<i>BDNF for PD</i>	313
<i>GDNF for PD</i>	313
<i>MANF for PD</i>	313
<i>Neurturin for PD</i>	314
<i>Platelet derived growth factor</i>	314
<i>Clinical trials with NTFs</i>	314
Nrf2-mediated neuroprotection in PD.....	315
Nuclear receptor-related 1:Retinoid X receptor α activation	315
Omega-3 polyunsaturated fatty acids	315
RAB3B overexpression.....	315
RNAi therapy for PD	316
Safinamide.....	316
Sirtuin 2 inhibitors for neuroprotection in PD	317
Squalamine and PD.....	317
Statins and PD.....	317
Targeting Bax.....	318
Vitamin D for neuroprotection in PD	318
Vaccine for PD	318
Clinical trials of neuroprotection in Parkinson's disease	319
Evaluation of neuroprotective therapies for PD	320
Current status and future challenges for neuroprotection in PD	322

8. Neuroprotection in Alzheimer Disease	323
Introduction	323
Pathomechanism of Alzheimer's disease	323
Role of glutamate transport dysfunction in AD	324
Role of neurotrophic factors in the pathomechanism of AD	324
Management of Alzheimer's disease	324
Neuroprotection in Alzheimer's disease.....	325
Inhibition of Aβ formation and aggregation.....	326
AN-1792	326
Clioquinol.....	327
Colostrinin	327
FKBP52 for neuroprotection from Cu toxicity in AD	328
Monoclonal antibody m266.....	328
Phenserine.....	328
Secretase inhibitors.....	329
Inhibition of neuroinflammation	329
Etanercept	329
Neurotrophic factors for neuroprotection in AD	330
AL-108	330
NGF gene therapy	330
Small molecule compounds binding to neurotrophin receptor p75NTR.....	331
Targeting plasminogen activator inhibitor type-1 gene.....	332
Estrogen and AD	332
Antioxidants	333
NSAIDS	333
Melatonin for AD	333
Memantine.....	333
Dimebon	334
Cerebrolysin	335
Curcumin as a neuroprotectant in Alzheimer disease	335
Ginko biloba.....	335
Tetrahydrocannabinol for neuroprotection in AD	336
Ladostigil tartrate.....	337
Phosphodiesterase inhibitors as neuroprotectives.....	337
PPAR-γ agonists	337
Role of statins in reducing the risk of AD	338
Combined therapeutic approaches to AD	338
Clinical trials in AD.....	338
Future prospects of neuroprotection in AD	346

Mild cognitive impairment	347
Relation of MCI to AD	347
Neuroprotection in MCI	348
9. Neuroprotection in Huntington Disease	349
Introduction	349
Pathophysiology of HD.....	349
Management of Huntington's disease	351
Neuroprotection in Huntington's disease.....	351
Antipsychotic D ₂ and 5-HT _{1A} antagonists	352
Caspase inhibitors.....	352
Clioquinol for HD.....	353
Creatine for stabilizing bioenergetic defects.....	353
Cysteamine.....	353
Drugs that block inappropriate calcium release from neurons	353
Enhancing protease activity for clearance of mHtt	354
Eicosapentaenoic acid.....	354
Free radical scavengers	354
Histone deacetylase inhibitors	355
Inhibitors of polyglutamine aggregation HD.....	355
Metal-protein attenuating compounds.....	356
Pridopidine.....	356
RRAS signaling pathway inhibition.....	356
Simvastatin as a neuroprotective in HD	357
Single chain Fv antibodies.....	357
SIRT1 activators for neuroprotection in HD	357
SIRT2 inhibitors for neuroprotection in HD	358
Synaptic activation of NMDA receptors.....	358
Targeting mutant huntingtin protein.....	358
Tetrabenazine	359
Combinatorial therapy and targeting multiple pathways in HD	359
Cell therapy for HD	359
<i>Cell transplants for HD.....</i>	<i>359</i>
<i>Stem cell-based therapy for HD</i>	<i>360</i>
Neurotrophic factors and gene therapy	361
RNAi and antisense therapies for Huntington's disease	361
10. Neuroprotection in Amyotrophic Lateral Sclerosis	363
Introduction	363
Pathophysiology of ALS	363
Neuroprotective therapies for ALS.....	368
Activated protein C	369
AEOL 10150.....	369
AIMSPRO	369
Anakinra.....	370
Antisense therapy	370
Arimoclomol for ALS.....	370
Ceftriaxone for ALS.....	371
Coenzyme Q10 for ALS.....	371
COX-2 inhibitors for ALS	371
Creatine for ALS	372
Dexpramipexole.....	372
Diallyl trisulfide.....	372
Edaravone for ALS	373
Erythropoietin for ALS	373
Gene therapy for ALS	373
Glatiramer acetate	374
GM602	374
Insulin-like growth factor.....	374
Ketogenic diet for neuroprotection in ALS.....	375
Lenalidomide.....	375
Lithium for neuroprotection in ALS	376
Masitinib	376
Melatonin for ALS.....	376
Methylcobalamin.....	377
Minocycline for ALS	377
Olesoxime as neuroprotective for ALS.....	377
ONO-2506 for ALS	377
Riluzole	378
RNAi-based therapy for ALS	378
Sodium phenylbutyrate.....	378

Stem cell therapy.....	379
<i>Clinical applications</i>	379
<i>Stem cell-based drug discovery for ALS</i>	379
<i>Suppressors of mTDP-43 toxicity</i>	380
Talampanel	380
Tamoxifen.....	381
Vaccination for ALS caused by SOD1 mutations	381
Vascular endothelial growth factor for ALS	381
Vitamin E for ALS.....	382
Clinical trials of neuroprotective therapies for ALS	382
Concluding remarks and future prospects	385

11. Neuroprotection in Miscellaneous Neurological Disorders 387

Introduction	387
Neuroprotection in synaptopathies	387
Neuroprotection in fragile X syndrome	388
Neuroprotection in dementia	388
Age-related dementia	388
<i>Aging brain and oxidative stress</i>	389
<i>Enhancing endogenous neurotrophic support of the aging brain</i>	389
<i>Hsp70 and age-related neurodegeneration</i>	389
<i>Pharmacological approaches for treatment of age-related dementia</i>	390
<i>Physical exercise to prevent decline of mental function with aging</i>	391
Vascular dementia	391
<i>Prediction of dementia in persons with vascular risk factors</i>	391
<i>Management of subcortical vascular dementia</i>	392
Dementia with Lewy bodies	393
Neuroprotection in AIDS dementia	393
Multiple system atrophy	394
Epilepsy	394
Mechanisms of neuronal damage in epilepsy	394
Strategies for neuroprotection in epilepsy	395
AEDs and neuroprotection.....	396
Cell therapy for neuroprotection in epilepsy.....	397
<i>Cell therapy of posttraumatic epilepsy</i>	398
<i>Cell therapy for temporal lobe epilepsy</i>	398
<i>Cell therapy for pharmacoresistant epilepsies</i>	398
Gene therapy for neuroprotection in epilepsy	399
Hyaluronan-based preservation of brain ECS volume.....	400
Hypothermia for neuroprotection in status epilepticus.....	400
Ketogenic diet for prevention of seizures.....	400
miR-211 as an attenuator of cholinergic-mediated seizures	400
Multiple sclerosis	401
Introduction	401
Epidemiology of multiple sclerosis	401
Pathophysiology	401
Current management of multiple sclerosis	402
Specific therapies for MS based on pathomechanism	403
Neuroprotection in multiple sclerosis	403
Clinical trials of neuroprotective therapies for MS	405
Neuroprotection by control of progressive forms of multiple sclerosis	406
Neuroprotection by controlling autoimmune inflammation in the brain	406
Neuroprotection by sealing the BBB with imatinib	406
TRPM4 cation channel blockers	407
Remyelination for neuroprotection in multiple sclerosis	407
Agents for neuroprotection in multiple sclerosis	407
<i>Angiotensin-II inhibitors</i>	407
<i>Antigliutamate agents</i>	408
<i>Antioxidants for neuroprotection in MS</i>	408
<i>Antisense and RNAi approaches to MS</i>	408
<i>B cell depletion therapy</i>	408
<i>Cell therapy for multiple sclerosis</i>	409
<i>Cannabinoids for neuroprotection in MS</i>	412
<i>Cladribine</i>	412
<i>Curcumin as a neuroprotectant in multiple sclerosis</i>	412
<i>Cytokine-directed therapies in MS</i>	413
<i>Dalfampridine in MS</i>	413
<i>Dimethyl fumarate</i>	413
<i>DNA vaccine for MS</i>	414
<i>Erythropoietin as a neuroprotective in MS</i>	414
<i>Fingolimod</i>	414

<i>Fusokine composed of GM-CSF and IL-15 for immune suppression</i>	415
<i>Gene therapy for MS</i>	415
<i>Ibudilast for MS</i>	416
<i>Iron chelators</i>	416
<i>IVIg for MS</i>	416
<i>Kinase inhibitors</i>	417
<i>Laquinimod</i>	417
<i>Melatonin for MS</i>	417
<i>Minocycline for MS</i>	417
<i>Monoclonal antibodies for MS</i>	418
<i>Natalizumab</i>	419
<i>Natural human antibodies for repair of myelin</i>	419
<i>Neurotrophic factors for multiple sclerosis</i>	420
<i>Nimodipine</i>	421
<i>Oral immunomodulatory agents for MS</i>	421
<i>Protein kinase Cβ as a therapeutic target for stabilizing BBB in MS</i>	421
<i>Recombinant T-cell ligands</i>	421
<i>Statins for MS</i>	422
<i>Teriflunomide</i>	422
<i>Tolerance-directed immunotherapy for MS</i>	422
Concluding remarks and future prospects for neuroprotection in MS	423
Neuroprotection in anti-NMDA receptor encephalitis	424
Neuroprotection in transverse myelitis	424
Neuroprotection in decompression sickness	424
Neuroprotection in victims of drowning	425
Neuroprotection in CSF circulatory disorders	426
Neuroprotection in hydrocephalus	426
Neuroprotection in normal pressure hydrocephalus	426
Neuroprotection in infections of the CNS	427
Neuroprotection in bacterial meningitis	427
<i>Mechanism of neural injury in bacterial meningitis</i>	427
<i>Strategies for neuroprotection</i>	428
Neuroprotection in cryptococcal meningitis.....	428
Neuroprotective approach to rabies.....	429
Neuroprotection in cerebral malaria.....	429
Neuroprotection in complications of systemic disorders	429
Neurological complications of cardiovascular disorders.....	429
<i>Neuroprotection after myocardial infarction</i>	429
<i>Neuroprotection in hypertensive encephalopathy</i>	430
<i>Management of hypertension to prevent dementia</i>	430
Neuroprotection in complications of diabetes	431
<i>Neuroprotection in hypoglycemic coma</i>	431
<i>Neuroprotection in diabetic retinopathy</i>	432
Neurological complications of liver disorders.....	432
<i>Hepatic encephalopathy</i>	432
<i>Bilirubin encephalopathy</i>	433
Neuroprotection in neurological complications of renal disease.	434
Neuroprotection in toxic encephalopathies	435
Encephalopathy due to organophosphorus poisoning	435
Neuroprotection against chemotherapy-induced brain damage	435
Neuroprotection against alcohol	436
<i>Alcoholic neurologic disorders</i>	436
<i>Fetal alcohol syndrome</i>	436
<i>Pathogenesis of alcohol-induced damage to the nervous system</i>	437
<i>Neuroprotection against neurotoxicity of alcohol</i>	437
Neuroprotection against exposure to therapeutic radiation	437
Neuroprotection against radiation encephalopathy	437
Role of SOD in protection again radiation-induced hippocampal dysfunction	438
Catalase reduces mitochondrial ROS for neuroprotection from proton irradiation.....	438
Neuroprotection in hypoxia-ischemia	439
Neuroprotection in neonatal hypoxic-ischemic brain injury	439
<i>Pathomechanism of neonatal hypoxic-ischemic brain injury</i>	439
<i>Management of neonatal hypoxia-ischemia</i>	440
<i>Approaches to neuroprotection in neonatal hypoxia-ischemia</i>	440
<i>Hyperbaric oxygen for neonatal hypoxia-ischemia</i>	440
<i>Hyperthermia for neonatal hypoxia-ischemia</i>	441
<i>Melatonin for neonatal hypoxia-ischemia</i>	441
<i>Minocycline for neonatal hypoxia-ischemia</i>	441
<i>Nicotinamide mononucleotide adenylyl transferase 1</i>	441
<i>Nitric oxide inhalation for neonatal hypoxia-ischemia</i>	442
<i>Plasminogen activator inhibitor-1 for neonatal hypoxia-ischemia</i>	442

<i>Recombinant erythropoietin for neonatal hypoxia-ischemia</i>	442
Neuroprotection in carbon monoxide poisoning	442
<i>Pathomechanism of CO poisoning as a basis for neuroprotection</i>	443
<i>Management of CO poisoning</i>	444
Neuroprotection after cardiac arrest	444
Syndrome of delayed post-hypoxic leukoencephalopathy	445
Neuroprotection of the fetus	445
Neuroprotection in sleep apnea	446
Neuroprotection in mitochondrial dysfunction	446
Mitochondrial permeability transition	447
Mitochondrial approaches for neuroprotection.....	447
Methylene blue	448
Role of nanolasers in evaluation of mitochondrial neuroprotectants	448
Neuroprotection in mitochondrial encephalopathies	448
Neuroprotection in psychiatric disorders	449
Cognitive impairment in schizophrenia.....	449
Electroconvulsive therapy and neuroprotection	449
Neuroprotection in schizophrenia	450
Neuroplasticity and neuroprotection in stress-induced psychiatric disorders.....	450
Neuroprotection in hearing loss	451
Causes of hearing loss	451
Pathomechanism of hearing loss	452
Prevention and treatment of hearing loss	452
<i>Hyperbaric oxygen for hearing loss</i>	452
<i>Stem cell therapy for hearing loss</i>	453
<i>Auditory hair cell replacement by gene therapy</i>	453
<i>Pharmaceutical approaches to hearing loss</i>	454
Neuroprotection of peripheral nerves	455
Neuroprotective agents for peripheral nerves	455
<i>Acetyl-L-carnitine for peripheral nerve injuries</i>	456
<i>Atorvastatin for peripheral nerve injuries</i>	456
<i>Erythropoietin for neuroprotection in peripheral nerve injuries</i>	456
Neuroprotection in peripheral nerve injuries	457
<i>Role of hyperbaric oxygen in peripheral nerve injuries</i>	457
<i>Role of neurotrophic factors in peripheral nerve injuries</i>	457
<i>Pharmacological approaches to Schwann cells</i>	457
<i>Role of gene therapy in neuroprotection of injured peripheral nerves</i>	457
<i>Schwann cell transplantation for peripheral nerve injury</i>	458
<i>Targeting Wallerian degeneration slow protein for neuroprotection</i>	458
Peripheral neuropathy	458
<i>Neuroprotection in diabetic neuropathy</i>	458
<i>Cell therapy for neuroprotection in diabetic neuropathy</i>	459
<i>Gene therapy with zinc finger DNA-binding proteins</i>	459
<i>Neuroprotection in chemotherapy-induced neuropathy</i>	459
Chronic inflammatory demyelinating polyradiculoneuropathy.....	460
<i>Neuroprotection in CIDP</i>	460
12. Neuroprotection of the Optic nerve and the Retina	461
Introduction	461
Optic neuropathy	461
Pathophysiology	461
Neuroprotection in optic neuritis	462
<i>Evaluating efficacy of drugs for optic neuritis</i>	463
<i>Flupirtine</i>	463
<i>Sodium channel blockers</i>	464
<i>Resveratrol</i>	464
Neuroprotection in optic nerve trauma	464
Potential regeneration of the optic nerve.....	465
Subthreshold transpupillary thermotherapy for protection of RGCs.....	465
Neuroprotection of optic nerve in glaucoma	465
Aminoguanidine as a neuroprotective in glaucoma	467
Antiglutamate agents for neuroprotection of optic nerve	467
Betaxolol	467
NGF eye drops.....	467
Targeting A β in glaucoma treatment.....	468
TNF- α blockers for neuroprotection in glaucoma	468
Concluding remarks about neuroprotection in glaucoma.....	468
Neuroprotection in retinal ischemia	468
β -adrenoceptor antagonists.....	469
Brimonidine as a neuroprotective in ischemic retinopathy	469
Endogenous neuroprotection in the retina	470

Erythropoietin for neuroprotection of retinal ischemia	470
Gene therapy for retinal neuroprotection.....	470
Hyperbaric oxygen for central retinal artery occlusion.....	471
Levodopa for treating non-arteritic anterior ischemic optic neuropathy	471
Thioredoxin as a neuroprotective agent in retinal ischemia.....	471
Protection against oxygen-induced retinopathy	471
Neuroprotection in macular degeneration	472
Epidemiology.....	472
Pathomechanism of AMD	472
Current treatment of AMD.....	472
Novel neuroprotective strategies against retinal degeneration	474
Antiangiogenic agents	475
Humanized MAb against A β	475
LXR agonists	476
Neurotrophic factors for neuroprotection in AMD	476
<i>CNTF for neuroprotection in AMD</i>	<i>476</i>
<i>N-acetylserotonin derivatives</i>	<i>476</i>
Nutritional protection against AMD	476
Progestogenic hormones.....	477
Protection of retinal cells from oxidative-stress-induced apoptosis.....	477
Sulindac	477
Tandospirone	478
Cell therapy for macular degeneration	478
<i>Retinal pigment epithelial cells.....</i>	<i>478</i>
<i>Stem cells.....</i>	<i>478</i>
<i>Neural progenitor cells.....</i>	<i>478</i>
Gene therapy for retinal degeneration	479
RNAi-based treatments for AMD.....	479
Neuroprotection in proliferative diabetic retinopathy	480
RNAi-based approaches to diabetic retinopathy.....	480
Clinical trials for optic nerve and retinal neuroprotection	481
13. Neuroprotection during Anesthesia and Surgery	483
Introduction	483
Anesthetic agents as neuroprotectives	483
Barbiturates	483
<i>Thiopental.....</i>	<i>484</i>
Etomidate	485
Propofol.....	485
Ketamine	485
Gaseous anesthetics.....	486
<i>Isoflurane</i>	<i>486</i>
<i>Xenon.....</i>	<i>486</i>
Local anesthetics	487
Monitoring of CNS function during anesthesia and surgery	487
Monitoring of cerebral function	487
Monitoring of spinal cord function during spinal surgery.....	487
Perioperative neuroprotection	488
Neuroprotection during cardiovascular procedures	489
CNS complications of cardiac surgery	489
Neuroprotective strategies during cardiac surgery.....	490
<i>Neuroprotection before anticipated or induced cardiac arrest.....</i>	<i>491</i>
<i>Neuroprotection during coronary artery bypass grafting.....</i>	<i>491</i>
<i>Preconditioning with hyperbaric oxygen.....</i>	<i>492</i>
<i>Neuroprotection in aortic surgery.....</i>	<i>492</i>
<i>Pharmacologic strategies for neuroprotection in aortic surgery.....</i>	<i>493</i>
Cerebral protection during organ transplantation surgery.....	493
Cerebral protection during neurosurgery	494
Cerebral angiography and endovascular surgery	494
Cerebral protection during surgery for arteriovenous malformations.....	494
Cerebral protection during surgery of intracranial aneurysms	494
Management of subarachnoid hemorrhage	495
<i>Vasospasm associated with subarachnoid hemorrhage.....</i>	<i>495</i>
Cerebral protection during carotid endarterectomy.....	497
Cerebral protection during surgery of brain tumors	497
Neuroprotective measures prior to surgery.....	498
<i>HBO preconditioning for neuroprotection during surgery</i>	<i>498</i>
Neuroprotection following surgery.....	498
<i>Neuroprotection by cranioplasty after decompressive craniectomy</i>	<i>499</i>
14. Markets for Neuroprotective Therapies.....	501

Introduction	501
The financial burden of CNS damage	501
Markets for neuroprotective therapies.....	501
Markets according to therapeutic areas.....	501
Stroke	502
CNS injury	502
Alzheimer disease	503
Parkinson disease	503
Multiple sclerosis.....	503
Epilepsy.....	503
Values of neuroprotective therapies in major world markets.....	503
Unmet needs in neuroprotectives.....	504
Future of neuroprotective therapies	505
Challenges in neuroprotective drug development	505
Promising areas of research in neuroprotection.....	506
Autoreactive antibodies	506
Biological therapies for neuroprotection	506
Multidisciplinary approaches to neuroprotection	507

15. References..... 509

Tables

Table 1-1: Historical landmarks in the development of neuroprotection	31
Table 1-2: Intrinsic neuroprotective factors.....	35
Table 1-3: Common features of pathophysiology of brain damage in diseases	43
Table 1-4: Place of neuroprotection in management of CNS disorders	45
Table 1-5: Indications for the use of neuroprotection	45
Table 1-6: Neuroprotective nanoparticles.....	51
Table 2-1: A classification of neuroprotective agents	55
Table 2-2: The neuroprotective effect of antiepileptic drugs	64
Table 2-3: Neuroprotective affect of minocycline in animal models.....	69
Table 2-4: Classification of antioxidants or free radical scavengers with neuroprotective potential.....	76
Table 2-5: Role of erythropoietin in the nervous system	82
Table 2-6: Ionotropic glutamate receptors	87
Table 2-7: Classification of metabotropic glutamate receptors (mGluRs).....	88
Table 2-8: Methods for neuroprotection based on nonpharmacological preconditioning	140
Table 3-1: Cerebrovascular diseases that are relevant to neuroprotection.....	143
Table 3-2: Neuroprotective strategies for stroke	153
Table 3-3: Selected effective combinations of hypothermia with other neuroprotective strategies for the treatment of ischemic stroke in experimental models	184
Table 3-4: Neuroprotective gene transfer in models of cerebral ischemia	191
Table 3-5: Neuroprotective gene therapy in animal stroke models	191
Table 3-6: Neuroprotective agents in clinical development for acute cerebrovascular disease	194
Table 3-7: Some failed trials for neuroprotective therapy for stroke	197
Table 3-8: Preclinical assessment of neuroprotective agents in acute stroke models.....	206
Table 4-1: Classification of closed TBI	211
Table 4-2: Current conventional management of traumatic brain injury	220
Table 4-3: Neuroprotective strategies for traumatic brain injury	222
Table 4-4: Intrinsic factors that influence regeneration in the central nervous system	240
Table 4-5: A classification of approaches to regeneration of the brain following injury	241
Table 4-6: Ongoing or completed clinical trials for neuroprotection in TBI	243
Table 4-7: Discontinued or failed clinical trials for neuroprotection in TBI.....	244
Table 5-1: Secondary mechanisms in spinal cord injury.....	249
Table 5-2: Neuroprotective and regenerative approaches for SCI.....	250
Table 5-3: Clinical trials for neuroprotection in SCI	265
Table 6-1: Neurodegenerative disorders with dementia	275
Table 6-2: Drugs in clinical trials for spinal muscular atrophy	281
Table 6-3: Approaches to neuroprotection in CJD.....	283
Table 6-4: Glutamate-based therapies in clinical development for neurodegenerative disorders.....	285
Table 7-1: Prevalence of Parkinson's disease in major markets 2016-2026	287
Table 7-2: Factors in the etiology of Parkinson's disease.....	287
Table 7-3: Strategies for the treatment of Parkinson's disease	295
Table 7-4: Current clinical trials of neuroprotective therapies for Parkinson disease	319
Table 7-5: Failed clinical trials of neuroprotective therapies for Parkinson disease.....	319
Table 7-6: Evaluation of neuroprotective agents for PD	321
Table 8-1: Cholinergic approaches to the treatment of Alzheimer's disease	325
Table 8-2: Neuroprotective agents for Alzheimer's disease.....	325
Table 8-3: Clinical trials for neuroprotection in Alzheimer disease	338
Table 8-4: Discontinued, failed or inconclusive clinical trials of Alzheimer disease	343
Table 8-5: Strategies for discovery of neuroprotective therapies for AD	346
Table 9-1: Neuroprotective approaches in HD.....	351

Table 10-1: Hypotheses for the pathogenesis of amyotrophic lateral sclerosis	363
Table 10-2: Genetic diagnostic biomarkers of ALS.....	366
Table 10-3: Classification of neuroprotective agents for amyotrophic lateral sclerosis	368
Table 10-4: Clinical trials of neuroprotective therapies for ALS	382
Table 10-5: Failed or discontinued trials of neuroprotective therapies for ALS.....	383
Table 11-1: Therapeutic approaches to subcortical vascular dementia	392
Table 11-2: Pharmacological neuroprotection against the sequelae of seizures	396
Table 11-3: Neuroprotective effect of AEDs in animal models of status epilepticus (SE)	397
Table 11-4: Specific therapies for MS based on postulated pathomechanisms.....	403
Table 11-5: Approved neuroprotective therapies for multiple sclerosis.....	404
Table 11-6: Neuroprotective therapies for multiple sclerosis in clinical trials	405
Table 11-7: Measures to prevent acute bilirubin encephalopathy	434
Table 11-8: Approaches to neuroprotection in neonatal hypoxia-ischemia	440
Table 11-9: Drugs with neuroprotective effect at mitochondrial level.....	447
Table 11-10: Causes of sensorineural hearing impairment	451
Table 11-11: Strategies for prevention and treatment of sensorineural hearing loss	452
Table 11-12: Agents for neuroprotection of the peripheral nervous system	455
Table 12-1: Causes of optic neuropathy.....	461
Table 12-2: Clinical trials of neuroprotective therapies in optic neuritis	463
Table 12-3: Neuroprotection of the optic nerve in glaucoma	466
Table 12-4: Strategies for neuroprotection in retinal ischemia	469
Table 12-5: Novel neuroprotective strategies against retinal degeneration	474
Table 12-6: Clinical trials for retinal neuroprotection	481
Table 13-1: CNS complications associated with cardiac procedures	489
Table 13-2: Strategies for protection of the brain during cardiac surgery	490
Table 13-3: Medical and surgical methods of cerebral vasospasm management.....	496
Table 13-4: Neuroprotection by prevention of vasospasm	496
Table 14-1: Neuroprotective market values 2016-2026	502
Table 14-2: Values of neuroprotective therapies in major world markets from 2016-26	503

Figures

Figure 2-1: Mechanism of neuroprotective effect of sigma-1 receptor agonists	63
Figure 2-2: NMDA receptor ion channel complex.....	91
Figure 2-3: Neuroprotective effect of galantamine	114
Figure 3-1: Some steps in the ischemic cascade and site of action of neuroprotectives	144
Figure 3-2: Relationship between dementia and acute ischemic stroke	152
Figure 3-3: A roadmap for neuroprotection	207
Figure 4-1: Cascade of events following traumatic brain injury	213
Figure 4-2: Neurometabolic cascade of mild TBI	214
Figure 4-3: Secondary injury mechanisms after TBI	215
Figure 4-4: Management of raised ICP after TBI	221
Figure 5-1: Pathomechanism of acute spinal cord injury	248
Figure 7-1: Neuroprotective strategies against death of dopamine-containing neurons in PD	293
Figure 9-1: Role of HTT protein in pathogenesis of HD and points of intervention.....	358
Figure 9-2: Antisense therapeutic approaches to HD for lowering huntingtin	362
Figure 11-1: A schematic overview of synaptopathies.....	387
Figure 11-2: Common mechanisms of neural damage in cerebral ischemia and seizures	395
Figure 11-3: Role of neuroprotection in epilepsy and its treatment.....	396
Figure 11-4: Mechanisms of neonatal hypoxia-ischemia and targets for neuroprotection.....	439
Figure 14-1: Unmet therapeutic needs in neuroprotective therapies	505