

Neuroprotection

Part I: Methods & Drugs

By

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

November 2021

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 with specialist qualifications including Fellowships of the Royal Colleges of Surgeons in Australia and Canada. He has trained, practiced and held academic positions in several countries including Switzerland, India, Iran, Germany Canada and USA. After retirement from neurosurgery, Prof. Jain remains a consultant in neurology. He is also working in the biotechnology/biopharmaceuticals industry and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of UK. Currently, he is the CEO of Jain PharmaBiotech.

Prof. Jain's 492 publications include 35 books (6 as editor+ 29 as author) and 50 special reports, which have covered important areas in biotechnology, gene therapy and biopharmaceuticals, biomarkers: proteomics, molecular diagnostics, nanobiotechnology, and personalized medicine. Contributions to MedLink, an accredited continuing education program for neurologists, include 172 articles out of a total of 1250 articles by 450 authors. These articles are updated on a yearly basis. Prof. Jain's earlier books were the first in the areas covered: "Handbook of Laser Neurosurgery" (Charles C. Thomas, Springfield, Ill, 1983) and "Textbook of Hyperbaric Medicine" (1st ed in 1990 and 6th ed by Springer, 2017). His "Textbook of Gene Therapy" was translated into Chinese in 2000. Recent books include "Handbook of Nanomedicine" (Springer 2008, Chinese edition by Peking University Press 2011, 3rd ed 2017), "Textbook of Personalized Medicine" (Springer 2009; Japanese ed 2012; 2nd ed Springer 2015, 3rd ed 2021), "Handbook of Biomarkers" (Springer 2010; Chinese ed, Chemical Industry Press 2016, 2nd ed 2017), "Drug-induced Neurological Disorders", 4th ed (Springer 2021), "Handbook of Neuroprotection" (Springer 2011, 2nd ed 2019), "Applications of Biotechnology in Cardiovascular Therapeutics" (Springer 2011), "Applications of Biotechnology in Neurology" (Springer 2013), and "Applications of Biotechnology in Oncology" (Springer 2014). He has also edited 3 editions of "Drug Delivery System" (Springer 2008, 20012 and 2020) and "Applied Neurogenomics" (Springer 2015). Lectures on personalized medicine given at Kazakh National Medical University, Kazakhstan were translated into Russian and published as a book "Essentials of Personalized Medicine" (LITERRA Publishing House, Moscow, 2019). Currently, he is writing "The Handbook of Alzheimer Disease" to be published by Springer in 2022.

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.

November 2021 (first edition published in April 2000)
Copyright © 2021 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.

T A B L E O F C O N T E N T S

0. Executive Summary	31
1. Introduction	35
Definitions	35
Historical development of neuroprotection	35
Neurophysiological basis of neuroprotection	36
Astrocytic glycogen-derived lactate as fuel for the brain.....	36
Gene expression in the human brain	36
Role of astrocytes in neuroprotection.....	37
Role of glymphatic system in neuroprotection.....	37
Role of sleep in neuroprotection.....	38
Role of cerebral metabolism in neuroprotection	38
Role of circadian genes in neuroprotection	38
Role of blood-brain barrier in neuroprotection.....	39
Role of the gut microbiota in development of integrity of the BBB	39
Intrinsic neuroprotective factors	39
Neuroprotective gene expression	41
<i>Upregulation of GADD34</i>	41
<i>Induction of NR4A proteins by CREB in neurons</i>	41
<i>Elevation PGC-1α for neuroprotection in PD.....</i>	41
Neurotrophic factors.....	42
Intrinsic nonenzymatic antioxidants	42
Activation of transcription factor Nrf2	42
Intrinsic neuroprotective factors	43
<i>aB-crystallin.....</i>	43
<i>Docosahexaenoic acid.....</i>	43
<i>Excitatory amino acid transporters</i>	43
<i>Extracellular serine protease thrombin.....</i>	43
<i>Galanin.....</i>	44
<i>Heat-shock proteins</i>	44
<i>Neuroglobin</i>	44
<i>Nuclear factor I-A</i>	45
<i>Prion protein</i>	45
<i>Rai adaptor protein</i>	46
Stem cell factor	46
Role of the immune system in neuroprotection	46
Induction of DNA repair enzymes for neuroprotection	47
Microtubule-based neuroprotective response to axonal injury	47
Pathomechanisms of CNS injury as basis for neuroprotection	48
Biomarkers of neurological disorders and neuroprotection.....	48
CNS biomarker identification using proteomics	49
Brain imaging for detection of biomarkers	49
Neuroprotection in cerebral hypoxia.....	49
Effects of hypoxia on the brain	50
<i>Cerebral Metabolism During Hypoxia</i>	50
Adaptive mechanisms in hypoxia	51
Neuroprotection in hypoxia-ischemia	51
Neuroprotection in neuroinflammation	52
Pathomechanism of neuroinflammation	52
<i>Role of microglia in neuroinflammation</i>	52
<i>Role of other players in neuroinflammation</i>	53
<i>Causes of neuroinflammation</i>	53
Biomarkers of neuroinflammation	54
<i>Brain imaging biomarkers of neuroinflammation</i>	54
Neuroprotection in mental stress.....	55
Neuroprotection in disruption of circadian rhythms.....	55
Role of neuroprotection in various neurological disorders	56
Neuroprotection and neuroregeneration.....	57
Acute versus chronic neuroprotection	57
Discovery and evaluation of neuroprotective agents	58
Neuroprotective drug discovery	58
Discovery of CNS drugs that penetrate the blood-brain barrier	58
In vitro assays for the evaluation of neuroprotective agents	59
Oxidative injury model to test neuroprotective drugs.....	59
Apoptosis model for designing neuroprotective drugs	60
Transgenic mouse models of neurological disorders.....	60
Evaluating effects of neuroprotective drugs on living brain slices.....	60
Role of brain imaging in neuroprotective drug discovery and development	61

<i>Positron emission tomography</i>	61
<i>Role of single photon emission computed tomography</i>	61
<i>Functional CT scanning to evaluate cerebrovascular protection</i>	62
<i>Magnetic resonance imaging for the evaluation of neuroprotectives</i>	62
Application of nanotechnology to neuroprotection	62
<i>Anthocyanin-loaded PEG-gold nanoparticles</i>	63
<i>Buckminsterfullerene C60 derivatives</i>	64
<i>Cadmium telluride nanoparticles prevent Aβ fibril formation</i>	64
<i>Ceria nanoparticles as antioxidants</i>	64
<i>Chitosan nanoparticles against oxidative stress.</i>	65
<i>Nanoparticles as carriers of neuroprotective agents into the brain</i>	65
<i>Polymer nanoparticles</i>	65
<i>Squalenoyl adenosine nanoparticles</i>	65
Evaluation criteria for potential neuroprotective agents.....	66
2. Neuroprotective Agents	67
Classification of neuroprotective agents	67
α2 adrenoreceptor agonists	71
Dexmedetomidine	71
Activated protein C	72
Activity-dependent neuroprotective protein	72
Davunetide	72
Adenosine analogs	73
Propentofylline	73
Antidepressants	73
Antidepressant-induced neurogenesis.....	73
Neurogenesis induced by electroconvulsive therapy	74
Neuroprotective effect of selective serotonin reuptake inhibitors	74
<i>Fluoxetine as a neuroprotective agent</i>	76
Antiepileptic drugs as neuroprotectives	76
BIS-001	77
Levetiracetam	77
Phenytoin	78
Valproic acid.....	78
Anti-neuroinflammatory agents	78
Aspirin.....	78
Interleukin-1 antagonists	79
COX-2 inhibitors	79
<i>Nimesulide</i>	80
Gold microparticles as anti-neuroinflammatory agents.....	80
Matrix metalloproteinase inhibitors as anti-neuroinflammatory agents	80
Minocycline	80
Prostaglandin receptor antagonists.....	81
Anti-apoptosis agents	82
Activated protein C	83
Calpain inhibitors	83
Caspase inhibitors.....	83
DNA binding drugs	83
Lithium	84
Melatonin.....	84
Olesoxime.....	84
Omega-3 fatty acids.....	85
<i>Docosahexaenoic acid</i>	85
Poly(ADP-ribose) polymerase inhibitors	85
Prevention of apoptosis by binding of proNGF to sortilin.....	86
Antioxidants/free radical scavengers	87
Free radical generation	87
Natural defenses against oxidative stress.....	87
Effects of oxidative damage	87
<i>Oxidative damage and aging</i>	87
<i>Neuronal damage by free radicals</i>	88
<i>Oxidative damage and neurodegenerative disorders</i>	88
Measures to control oxidative stress.....	89
<i>Categories of therapeutic antioxidants</i>	89
<i>Alpha-phenyl-tert-butylnitron</i>	90
<i>Coenzyme Q10</i>	90
<i>Dihydroergocryptine</i>	90
<i>Flavonoids</i>	91
<i>Mitochondria-targeted antioxidants</i>	91
<i>Neuroleptics as antioxidants</i>	91
<i>Nitrones</i>	92

<i>NRF2 for augmenting neuroprotection against oxidative stress</i>	92
<i>Nrf2/ARE-mediated antioxidant actions of pro-electrophilic drugs</i>	92
<i>Quercetin</i>	93
Translation of antioxidant neuroprotection from preclinical to clinical	93
Arimoclomol	93
Carbon monoxide and heme oxygenase	93
Cell transplants	94
Cells secreting neuroprotective substances	94
Stem cells	94
Stem cell activation for neuroprotection/regeneration by glucocorticoids	95
Use of neural stem cells to construct the blood brain barrier	95
Cytokines	95
Erythropoietin	95
<i>Non-erythropoietic EPO variants and mimics</i>	97
<i>Granulocyte colony-stimulating factor</i>	97
Delta-opioid receptor agonists	98
Delta opioid peptide-induced hibernation for neuroprotection	98
FK960	98
Gene therapy	99
Glucagon-like peptide	99
Glatiramer acetate	100
Glutamate antagonists	100
Neuroprotection by scavenging blood glutamate	101
Glutamate transporters	101
Glutamate transporter-mediated neuroprotective effect of drugs	102
Neuroprotection by targeting KAI subunit of kainate receptor	102
Glycine-proline-glutamate analogs	103
Hydrogen sulfide	103
Hibernation induced by hydrogen sulfide	103
NMDA receptor ion channel complex	104
NMDA receptor antagonists	106
<i>NMDA NR2B subunit receptor antagonists</i>	106
<i>Ifenprodil</i>	106
<i>Memantine as a neuroprotective agent</i>	106
<i>NAALADase inhibitors</i>	106
<i>Gacyclidine</i>	107
<i>N-alkylglycines</i>	107
AMPA receptor modulators	107
Metabotropic glutamate receptor modulators	108
Cannabinoids	108
Dexanabinol	109
Glutathione	109
Heat shock proteins	109
Histone deacetylase inhibitors for neuroprotection	110
Hormones	110
Estrogen and neuroprotection	110
<i>Neuroprotective effect of estrogen receptor ligands</i>	111
<i>Selective estrogen receptor modulators</i>	111
<i>Mitochondrial mechanisms of estrogen neuroprotection</i>	112
Insulin	112
Ion Channel modulators	113
Calcium channel blockers	113
<i>Ziconotide</i>	113
Na ⁺ channel blockers	114
Neuroprotective potassium channel inhibitors	114
Kynurenone inhibitors	114
Leukocyte adhesion inhibitors	115
Modafinil	116
Neurite outgrowth-promoting agents	116
Monoclonal antibodies	116
Neuroimmunophilins	116
Cyclosporin-A	117
FK506	117
Rapamycin	117
Neurotrophic factors	118
Activity-dependent neurotrophic factor	118
Bone morphogenetic proteins	118
Brain-derived neurotrophic factor	119
Ciliary neurotrophic factor	119
Fibroblast growth factors	119
Glial cell line-derived neurotrophic factor	120

Insulin-like growth factor	120
Nerve growth factor	121
Neurotrophins	122
Osteogenic protein-1	122
Pigment epithelium-derived factor	122
Transforming growth factor- β 1	122
Vascular endothelial growth factor	123
Neurotrophic factor-related neuroprotective agents	123
<i>Amitriptyline as a TrkA and TrkB receptor agonist</i>	123
<i>Colivelin</i>	123
<i>Gambogic amide</i>	124
<i>Inosine</i>	124
<i>Meteorin</i>	124
<i>Oxygen-regulated protein 150 kD</i>	124
<i>Prosaptide</i>	125
<i>Siagosome</i>	125
<i>Small molecule activators of the Trk receptors</i>	125
Nicotine and nicotinic receptor agonists	126
<i>Neuroprotective effect of galantamine mediated via $\alpha 7nAChRs$</i>	126
<i>Galantamine-induced Aβ clearance via $\alpha 7nAChRs$</i>	126
Nitric oxide-based neuroprotection	127
Nitric oxide synthase inhibitors	127
Nitric oxide mimetics	128
Nitric oxide donating derivatives	128
Nootropics	128
<i>Piracetam</i>	129
Nutraceuticals and naturally-derived compounds	129
Cinnamon	129
Coffee	130
Creatine	130
Curcumin/curry	130
<i>Mechanism of neuroprotective effect of curcumin</i>	131
Flavonoids	131
Glyceryltriacetate	131
Green tea	131
Herbal preparations	132
<i>Flavonoid wogonin</i>	132
<i>Ginseng</i>	132
Nicotinamide	132
Punicalagin from pomegranate	133
Resveratrol	133
Osmotic diuretics	134
Mannitol	134
Osteopontin	134
Oxygen therapeutics	135
Oxygen carriers	135
Hemoglobin-based oxygen carriers	135
Perfluorocarbons as oxygen carriers	136
Hyperbaric oxygen therapy	137
P7C3 compounds	137
Peptides	137
C3-derived peptide for neuroprotection and neuroregeneration	137
Corticotropin-releasing hormone	138
Thyrotropin-releasing hormone	138
Vasoactive intestinal peptide	138
Pharmacological preconditioning	139
PPARs as drug targets for neuroprotection	139
Proteins	140
Amyloid precursor protein	140
Protein kinase C activators	140
PSD-5 antagonists	141
Riluzole	141
Role of RNA interference in neuroprotection	141
Role of miRNA in neuroprotection	141
Sigma receptor agonists as neuroprotective agents	142
SIRT group of proteins	142
Statins	143
Steroids	144
Dehydroepiandrosterone	144
Sulforaphane	144
Tauroursodeoxycholic acid	145

Tetanus toxin as a neuroprotective agent.....	145
Thrombolytic agents as neuroprotective agents	145
Uncoupling protein 2	146
Vaccines as neuroprotectives	146
Vitamins as neuroprotective agents.....	146
Vitamin B12	146
Vitamin D	147
Unconventional biologicals	147
Non-pharmacological approaches to neuroprotection.....	147
Caloric restriction.....	148
Cerebral exercise	148
<i>Bilingualism for prevention of decline of mental function.....</i>	<i>148</i>
Electrical fields for improvement of cerebral function in neurodegeneration	148
Environmental enrichment	149
Hypothermia	149
<i>Limitations of hypothermia.....</i>	<i>150</i>
<i>Hypothermic neuroprotection in hypoxia-ischemia.....</i>	<i>150</i>
Ketogenic diet	151
Mediterranean diet	151
Nonpharmacological preconditioning for neuroprotection.....	152
Physical exercise.....	152
Suspended animation and neuroprotection.....	153
Transcranial magnetic stimulation	153
3. Neuroprotection in Cerebrovascular Disease	155
Introduction	155
Pathophysiology of cerebral ischemia.....	156
Calcium overload	156
Cerebral edema in stroke.....	156
Cytokines and adhesion molecules in stroke	157
<i>Adhesion molecules.....</i>	<i>157</i>
<i>Interleukin-1 and IL-6</i>	<i>157</i>
<i>Tumor necrosis factor-α.....</i>	<i>158</i>
DNA damage and repair in cerebral ischemia	158
Gene expression in response to cerebral ischemia	158
Glutamate as a biomarker of stroke	159
Heat shock proteins in stroke	159
Ion channel dysfunction in stroke.....	159
Neuroinflammation in cerebral infarction	159
Neurotrophic factors in stroke.....	160
<i>Problems requiring investigation of the role of NTFs in stroke</i>	<i>160</i>
Neurovascular dissociations after ministrokes	160
Nitric oxide in cerebral ischemia.....	161
Oxygen free radicals in cerebral ischemia.....	161
Poly(ADP-ribose) polymerase (PARP) gene	161
Protease-activated receptor 1	161
Effect on the brain of cessation of cerebral circulation	162
Reperfusion injury after cerebral ischemia	162
Neuroprotection according to zones in cerebral infarction.....	162
Zone of ischemic infarction.....	162
Penumbra	163
Current management of stroke.....	164
Neuroprotection in stenosis of intracranial arteries	164
Neuroprotection in stroke with intracerebral hemorrhage	164
Neuroprotection in cerebrovascular malformations	164
<i>Arteriovenous malformations.....</i>	<i>164</i>
<i>Cavernous cerebrovascular malformations</i>	<i>165</i>
Neuroprotective strategies for ischemic stroke in patients with dementia	165
Neuroprotection in transient ischemic attacks	166
Secondary prevention of stroke	166
Neuroprotective therapies for stroke.....	167
Neuroprotective strategies according to pathomechanism of stroke	168
Pharmacologic neuroprotective agents for stroke.....	169
α B-crystallin as a neuroprotectant in stroke	169
Acid-sensing ion channel blockers	169
Adrenergic receptor antagonists.....	169
AMPA receptor antagonists as neuroprotectives for stroke.....	169
Anesthetic agents as neuroprotectives in stroke.....	170
<i>Propofol as neuroprotective in stroke.....</i>	<i>170</i>
Antia apoptotic neuroprotectives	170
NIM811	170

<i>Creatine as neuroprotective in stroke</i>	171
<i>Lithium as a neuroprotective in stroke.....</i>	171
<i>TUDCA as a neuroprotective in stroke.....</i>	171
Antidepressants as neuroprotectives agents in stroke.....	172
<i>Fluoxetine as neuroprotectectant in stroke.....</i>	172
Antiepileptic drugs as neuroprotectives in stroke.....	172
<i>Tiagabine.....</i>	172
<i>Topiramate</i>	172
Anti-HMGB1 monoclonal antibody	173
Antiinflammatory agents.....	173
<i>Cox-2 inhibitors for ischemic stroke.....</i>	173
<i>Minocycline for neuroprotection in stroke</i>	173
Antioxidant approaches	174
<i>Carnosine as a neuroprotective in stroke.....</i>	174
<i>Dehydroascorbic acid.....</i>	174
<i>Tocotrienols</i>	175
<i>Uric acid</i>	175
Arimoclomol for stroke	176
Cardiac glycosides as neuroprotectives in stroke	176
Clenbuterol	176
Coagulation inhibitors as neuroprotectives	176
<i>Heparin and enoxaparin.....</i>	176
<i>Warfarin vs dabigatran</i>	177
<i>Apixaban</i>	177
Curcumin as a neuroprotectant in stroke.....	177
Docosahexaenoic acid for ischemic stroke	178
Ephrin-A5 blockers.....	178
Estrogen for stroke	178
Extendin-4	179
Flavones for neuroprotection in stroke	180
<i>Epicatechin</i>	180
<i>Isorhamnetin.....</i>	180
Glutamate clearance from blood	180
Hamartin induction by cerebral ischemia as a basis for neuroprotection	181
Histone deacetylase inhibitors for neuroprotection in stroke	181
Histamine H ₂ -receptor modulation.....	181
Inosine for stroke	182
Insulin-like growth factor-I.....	182
Intravenous immunoglobulin as neuroprotective in stroke	182
Ischemic preconditioning for neuroprotection in stroke	182
Ketone bodies for neuroprotection in stroke	183
Magnesium	184
Mineralocorticoid receptor blockade for neuroprotection.....	184
miR-223 and neuroprotection in stroke	184
NA-1 as neuroprotective against ischemic stroke	184
Nasal delivery of neuroprotective agents in stroke	185
Nerinetide	185
Neuroserpin as a neuroprotective in stroke	185
N-2-mercaptopropionyl glycine	186
NeuroAiD	186
Neurotrophic factors as neuroprotectives for stroke	186
<i>Brain-derived neurotrophic factor.....</i>	186
<i>Cerebral dopamine neurotrophic factor</i>	187
<i>Fibroblast growth factor.....</i>	187
<i>Granulocyte colony stimulating factor.....</i>	187
<i>Granulocyte-macrophage colony-stimulating factor</i>	188
<i>Glial cell line-derived neurotrophic factor</i>	188
<i>Insulin-like growth factor-1</i>	188
<i>Neuregulin-1</i>	189
<i>VEGFD delivered intranasally</i>	189
NO-based strategies for neuroprotection in cerebral ischemia	189
NOX-4 inhibitors for neuroprotection in stroke	189
Omega-3 fatty acids for neuroprotection after cerebral ischemia-hypoxia.....	190
Pannexin channel blockers for neuroprotection in stroke	190
Perlecan domain V	190
Peroxisome proliferator-activated receptor-γ agonists	190
<i>Pioglitazone for reduction of stroke risk</i>	191
PGE ₂ EP2 receptor activation	191
Progesterone	191
Proteoglycan-degrading enzymes.....	192
Proteosome inhibitors	192

Statins for prevention and neuroprotection in stroke	192
Sildenafil	193
Stroke vaccine.....	193
Thrombosis inhibitors	194
<i>Aspirin</i>	194
<i>Clopidogrel</i>	194
<i>Dipyridamole</i>	194
<i>Ticagrelor</i>	195
Thrombolytic therapy for acute stroke	195
<i>Tissue plasminogen activator as neurorestorative in stroke</i>	195
Vitamin E for neuroprotection in stroke.....	195
Neuroprotection in ischemia-reperfusion injury	196
Aminoguanidine.....	196
Dexmedetomidine	196
Methylene blue for neuroprotection in ischemia-reperfusion injury	197
Miscellaneous agents for neuroprotection in reperfusion injury.....	197
Neuroprotection by treatment of cerebrovascular malformations.....	197
<i>Arteriovenous malformations</i>	197
<i>Cerebral cavernous malformations</i>	198
Prevention of hemorrhage following ischemic stroke	198
Non-pharmacological neuroprotective therapies for stroke.....	199
Blood replacement for neuroprotection after cerebral ischemia in mice.....	199
Hypothermia for neuroprotection in acute stroke.....	199
Hyperbaric oxygen therapy for neuroprotection in acute stroke.....	200
Hypothermia combination with other neuroprotective strategies	201
Infrared laser therapy for ischemic stroke	201
Preconditioning for neuroprotection against cerebral ischemia	202
<i>Neuroprotection in ischemia/reperfusion injury</i>	202
Neurosurgical procedures for stroke.....	203
Neurosurgical procedures for neuroprotection in acute stroke.....	203
<i>Decompressive hemicraniectomy</i>	203
<i>Thrombectomy</i>	204
<i>Stenting</i>	205
<i>Multiple endovascular modalities</i>	205
Neurosurgical procedures for chronic cerebral ischemia	206
Neurostimulation of sphenopalatine ganglion	206
Stent versus surgery for asymptomatic carotid stenosis	207
Neurorehabilitation in relation to neuroprotection in stroke.....	207
Protective effect of physical activity on stroke in the elderly	207
Biological therapies for stroke	208
Cell therapy for stroke	208
<i>Stem cell transplant for stroke</i>	208
<i>Preconditioning with hyperbaric oxygen for stem cell therapy</i>	208
<i>Immortalized cell grafts for stroke</i>	209
<i>Stimulation of intrinsic stem cells for repair of brain in stroke</i>	209
Gene therapy for neuroprotection in cerebrovascular disease	209
Regulation of microRNAs for neuroprotection in cerebral ischemia.....	211
RNAi-based therapy for neuroprotection in stroke	211
Vaccines for neuroprotection in stroke	212
Neuroprotective therapies for cerebral ischemia: clinical trials	212
Albumin	213
Free radical scavengers	213
DP-b99	214
Mildronate.....	215
Perindopril	215
Failed clinical trials of neuroprotection in stroke	215
<i>Ancrod</i>	217
<i>Aptiganel</i>	217
<i>Cerovive</i>	217
<i>Citicoline</i>	218
<i>Desmoteplase</i>	219
<i>Erythropoietin as a neuroprotective in stroke</i>	220
<i>Selfotel</i>	220
<i>Lubeluzole</i>	221
<i>Nalmefene</i>	221
<i>Gavestinel</i>	221
<i>Nimodipine</i>	221
<i>Sipatrigine</i>	222
<i>Causes of failure of stroke trials</i>	222
Measures for prevention of failures in stroke trials	224
Design of acute stroke trial to facilitate drug approval	225

The ideal neuroprotective agent for stroke	225
Prevention of stroke	226
Concluding remarks and future of neuroprotection in stroke.....	226
4. Neuroprotection in Traumatic Brain Injury	229
Introduction	229
Cerebral hypoxia/ischemia as a complication of trauma.....	229
Epidemiology of TBI.....	229
TBI in the military	230
Pathophysiology of TBI.....	230
Immediate damage following TBI	232
Blast injury sequelae	232
Cerebral edema following TBI	232
Neurometabolic cascade after TBI	232
Delayed damage following TBI.....	233
Mechanism of axonal damage after TBI	234
Role of neuroinflammation in TBI	234
BBB damage after TBI	234
Molecular events following TBI.....	235
Chronic traumatic encephalopathy	235
Neurocognitive sequelae of TBI.....	237
Changes in neurotrophic factors following TBI	237
Changes in neurotransmitters following TBI.....	237
Proteomics of TBI	238
Genetic influences on outcome following TBI	238
Management of TBI	239
Management during acute phase of head injury	239
<i>Control of cerebral edema and intracranial pressure</i>	239
Corticosteroids	241
Decompressive craniectomy	241
Personalized approach to cerebral edema in TBI	241
Neuroprotection in TBI	241
Amantadine.....	243
Antioxidants	243
Barbiturates	243
β - and γ -secretase inhibitors	243
Beta blockers	244
Bradykinin B ₂ antagonists	244
Cell cycle inhibitors for TBI.....	244
COX-2 inhibitors for neuroprotection in TBI	244
Cyclosporin for neuroprotection in TBI	245
Dexanabinol for TBI	245
Erythropoietin for neuroprotection in TBI	246
Gold implants for neuroprotection in focal TBI	246
Histone deacetylase inhibitors for neuroprotection in TBI	246
Inhibitors of integrated stress response	246
Levosimendan	247
Magnesium sulfate	247
Minocycline for TBI.....	247
Multipotential neuroprotective agents for TBI	247
Neurotrophic factors for TBI	248
Neurosteroids as neuroprotective agents for TBI.....	249
NMDA receptor antagonists	249
<i>Neuroprotection in TBI against glutamate-induced excitotoxicity.....</i>	250
NP-1	250
Nogo-A inhibitor	250
Nutritional approaches to neuroprotection in TBI.....	250
<i>Branched chain amino acids to ameliorate cognitive impairment in TBI.....</i>	251
<i>Creatine for neuroprotection in TBI</i>	251
<i>Nicotinamide for neuroprotection in TBI</i>	252
<i>Omega 3 fatty acids as neuroprotectives in TBI</i>	252
Oxygen carriers for TBI.....	253
Polyethylene glycol for neuroprotection in TBI	253
Propofol for neuroprotection in TBI.....	253
Rapamycin as neuroprotective in TBI.....	254
Simvastatin as neuroprotective in TBI	254
Statins as neuroprotective agents in concussion	254
Targeting mitochondrial pathology in TBI	254
Thyrotropin-releasing hormone analogs	255
Tissue plasminogen activator.....	255
Biological approaches to neuroprotection in TBI	255

Antisense approaches to TBI	255
Cell therapy for TBI.....	256
<i>Limitations of stem cell therapy for acute TBI.....</i>	256
<i>Stem cell-derived exosomes for treatment of TBI.....</i>	257
Gene therapy for TBI.....	258
Vaccines for TBI.....	258
Non-pharmaceutical approaches to neuroprotection in TBI.....	258
Deep brain stimulation for TBI.....	258
Hyperbaric oxygen therapy for TBI.....	259
Hypothermia	259
Reduction of microglial migration after TBI.....	259
Vacuum for mechanical tissue resuscitation in TBI	260
Prophylactic neuroprotection against TBI.....	260
Role of helmets in protection against TBI	260
Role of physical exercise in protection against TBI	260
Neuroprotection against late sequelae of TBI.....	261
Antiepileptic drugs for prevention of seizures and neuroprotection	261
Neuroprotection during rehabilitation phase of TBI.....	261
Neuroregeneration following TBI.....	262
<i>Intrinsic factors that influence regeneration following TBI</i>	262
<i>Causes of lack of regeneration following TBI.....</i>	262
<i>Approaches to regeneration of the brain following TBI</i>	262
Clinical trials of neuroprotective agents in TBI	264
Ongoing clinical trials in TBI	264
Failed clinical trials in TBI.....	265
<i>Differences between clinical trials and studies in animal models of TBI</i>	265
<i>Subgroup analysis.....</i>	266
<i>Improving the clinical trial design.....</i>	266
<i>Clinical trials combining multiple treatment strategies</i>	266
<i>Shortening the trial time.....</i>	267
Conclusions and future of neuroprotection in TBI.....	267
5. Neuroprotection in Spinal Cord Injury	269
Introduction	269
Pathophysiology of SCI.....	269
Secondary mechanisms of SCI.....	270
Neurotrophic factor changes in SCI	271
Management of SCI	271
Pharmacological neuroprotective agents for SCI	272
4-aminopyridine	273
Antibodies as neurite growth inhibitors in SCI.....	273
Antiexcitotoxic agents	273
<i>Gacyclidine</i>	273
<i>GM-1 ganglioside</i>	274
Bacterial enzyme chondroitinase ABC	274
Docosahexaenoic acid as neuroprotective in SCI	274
Erythropoietin as a neuroprotective in SCI	274
Free radical scavengers for neuroprotection in SCI	274
Immunosuppressants as neuroprotectants in SCI	275
Interleukin-10 for neuroprotection in SCI	275
Matrix metalloproteinase inhibitors for SCI	275
Methylprednisolone	276
Minocycline as neuroprotective in SCI.....	276
Modulation of macrophage responses for neuroprotection after SCI.....	277
Neurotrophic factors for neuroprotection after SCI	277
<i>Fibroblast growth factors in the management of SCI</i>	278
<i>Promotion of regeneration of neurons in SCI</i>	278
Rho pathway and Rho antagonists in SCI	278
Riluzole and methylprednisolone as neuroprotectants in SCI	279
Selenium as a neuroprotective for SCI.....	279
Sialidase for enhancing recovery after SCI	279
Targeting the inflammatory response for neuroprotection in SCI	280
Uric acid as neuroprotective in SCI.....	280
Non-pharmacological approaches to SCI	280
Hyperbaric oxygen therapy	280
Hypothermia for SCI	280
Cell therapy for SCI	281
Fetal neural grafts for SCI.....	281
Olfactory-ensheathing cells for SCI	281
Oligodendrocyte precursor cells for treatment of SCI.....	282
Schwann cell transplants for SCI.....	283

Transplantation of glial cells for SCI	283
Stem cells for SCI	283
<i>Bone marrow stem cells for SCI.....</i>	<i>283</i>
<i>Transplantation of ESCs for SCI.....</i>	<i>283</i>
<i>Transplantation of induced pluripotent stem cells in SCI</i>	<i>283</i>
<i>Transplantation of MSCs for SCI</i>	<i>284</i>
<i>Transplantation of NSCs for SCI.....</i>	<i>284</i>
<i>Transdifferentiation of stem cells into cholinergic neurons for SCI</i>	<i>285</i>
Gene therapy for SCI	285
Combined approaches to spinal cord injury	286
Discovery of new targets for neuroprotective therapies in SCI.....	287
Clinical trials in SCI.....	287
Concluding remarks	288
6. Neuroprotection in Neurodegenerative Disorders.....	289
Introduction	289
Pathomechanism of neurodegeneration	289
Aging and neurodegeneration	289
α -synuclein in neurodegeneration and neuroprotection	290
Dysregulation of cyclin-dependent kinase 5	291
Dysregulation of translation	291
Exosomes in CNS neurodegeneration and neuroregeneration.....	291
Genomics of neurodegenerative diseases.....	291
Impairment of neural transport in neurodegenerative disorders	292
Lack of neurotrophic factors	292
Mitochondrial damage leading to apoptosis	292
Neuroinflammation in neurodegenerative disorders	293
Neurodegeneration associated with chronic repeated cerebral injuries	293
Neurodegeneration associated with protein misfolding	293
<i>Modulation of neurodegeneration by molecular chaperones</i>	<i>293</i>
<i>Intrabodies targeting protein misfolding in neurodegeneration.....</i>	<i>294</i>
<i>Targeting proteins aggregation to prevent amyloid formation</i>	<i>294</i>
<i>Tau and neurodegeneration.....</i>	<i>294</i>
Role of apoptosis in neurodegenerative disorders.....	295
Role of glia in neurodegeneration.....	295
Role of metals in neurodegeneration	295
Spread of neurodegeneration	295
TDP-43 proteinopathy and neurodegenerative diseases	296
Viral infections and neurodegeneration	296
<i>AIDS and the nervous system</i>	<i>296</i>
<i>Avian influenza as cause of neurodegeneration</i>	<i>297</i>
Neurodegenerative disorders with dementia	298
Dementia with Lewy bodies.....	298
Frontotemporal dementia.....	299
Progressive supranuclear palsy.....	300
Genetic disorders with neurodegeneration	300
Batten disease.....	300
<i>Cell and gene therapies</i>	<i>300</i>
<i>Cerliponase alfa</i>	<i>301</i>
Familial dysautonomia	302
Friedreich ataxia.....	302
<i>Pathomechanism of FA</i>	<i>302</i>
<i>Neuroprotection in FA.....</i>	<i>302</i>
Leigh syndrome	303
Niemann-Pick type C disease.....	303
Spinal and bulbar muscular atrophy	304
<i>Spinal muscular atrophy</i>	<i>304</i>
Creutzfeldt-Jakob disease.....	306
Neuroprotection in Creutzfeldt-Jakob disease	306
<i>Pharmacological neuroprotectants against CJD</i>	<i>307</i>
<i>Innovative approaches to neuroprotection in CJD and future prospects.....</i>	<i>308</i>
Approaches to neuroprotection in neurodegenerative disorders.....	308
Glutamate-based therapies for neurodegenerative disorders	309
Histone deacetylase inhibitors for neurodegenerative disorders.....	309
Intermittent fasting for neuroprotection	310
Iron chelation for neuroprotection	310
Mitochondria permeability transition pore complex and neuroprotection.....	310
Modulation of proteostasis in neurodegenerative disorders	311
Targets to limit protein aggregation in neurodegenerative diseases	311
7. Neuroprotection in Parkinson Disease	313

Introduction	313
Epidemiology of Parkinson's disease	313
Pathophysiology of Parkinson's disease	313
Alteration of dopamine homeostasis	314
Apoptosis.....	314
Calcium interaction with α -synuclein.....	314
Disruption of iron homeostasis.....	315
Excitotoxicity.....	315
Genes and PD.....	315
Histone deacetylase 4 as a regulator of progression of PD	317
Oxidative stress.....	317
Propagation of pathologic α -synuclein from the gut to the brain in PD	318
Role of neurotrophic factors	318
Role of misfolding proteins	318
Role of α -synuclein in dementia of PD	319
Synaptic vesicle glycoprotein 2C disruption in PD	319
Neuroprotective strategies for PD based on pathomechanism.....	319
A genetic animal model of PD for testing neuroprotective strategies	320
Aldehyde dehydrogenase 1 protects nigrostriatal dopaminergic neurons	320
RNAi screening to identify neuroprotective genes in a PD model	321
Strategies to stop aggregation of α -synuclein	321
Targeting mitochondrial dysfunction in PD	321
Management of Parkinson's disease	322
Limitation of conventionally administered dopamine therapy	323
Neuroprotective therapy in PD.....	324
Neuroprotective effect of currently used drugs for PD	324
Pramipexole	324
Rasagiline mesylate	325
Ropinirole	326
Rivastigmine for treatment of dementia and falls associated with PD	326
Selegiline	327
Non-pharmacological strategies for neuroprotection in PD.....	327
Deep brain stimulation for PD	327
Effect of exercise and environmental enrichment on PD	328
Calorie restriction in PD	328
Development of neuroprotective therapies for PD	329
2B3-201 for targeted delivery of methylprednisolone.....	329
9-methyl- β -carboline.....	329
Adenosine A _{A2} receptor antagonists	329
Ambroxol.....	330
Antia apoptotic strategies for PD	330
ATP13A2 activation	330
Atremorine.....	331
Augmenting CNS glucocerebrosidase activity.....	331
β 2-Adrenoreceptor agonists	331
BT13 as GDNF receptor agonist	332
Calcium channel blockers for PD	332
Cell therapies for PD.....	332
<i>Stem cells for PD</i>	<i>332</i>
<i>Activation of endogenous stem cells and neural precursors</i>	<i>333</i>
<i>Pluripotent stem cell-derived neurons.....</i>	<i>333</i>
<i>Transplantation of iPSC-derived neural progenitors</i>	<i>334</i>
Cogane.....	334
Conserved dopamine neurotrophic factor for PD.....	335
Doxycyline as a neuroprotectant in PD.....	335
Farnesol	335
Free radical scavengers for neuroprotection in Parkinson's disease.....	336
<i>Antioxidants</i>	<i>336</i>
<i>Diapocynin.....</i>	<i>336</i>
<i>Tea extracts as neuroprotectives.....</i>	<i>336</i>
Gene therapy for PD.....	336
<i>Implantation of genetically engineered cells</i>	<i>337</i>
<i>Gene therapy using GDNF.....</i>	<i>338</i>
<i>Parkin gene therapy</i>	<i>339</i>
<i>Viral vector-based ubiquitination to prevent spread of α-synuclein</i>	<i>339</i>
<i>Concluding remarks about gene therapy for PD.....</i>	<i>340</i>
Heat shock protein 70	340
Liver X receptor β agonists.....	341
Melatonin as a neuroprotectant in PD	341
Nicotine as a neuroprotective in PD	341
Nilotinib for PD	342

Neuroprotective effect of leucine-rich repeat kinase-2 inhibitors	342
Neuroprotective effect of DJ-1 protein	342
Neurotrophic factors.....	343
<i>Basic fibroblast growth factor for PD.....</i>	343
<i>BDNF for PD.....</i>	343
<i>GDNF for PD.....</i>	343
<i>MANF for PD.....</i>	344
<i>Neurturin for PD</i>	344
<i>Platelet derived growth factor.....</i>	345
Nrf2-mediated neuroprotection in PD.....	345
Nuclear receptor-related 1:Retinoid X receptor α activation.....	345
Omega-3 polyunsaturated fatty acids	345
RAB3B overexpression.....	346
Resveratrol for PD.....	346
RNAi therapy for PD	346
Safinamide.....	347
Sirtuin 2 inhibitors for neuroprotection in PD	348
Squalamine and PD	348
Statins and PD.....	348
Targeting Bax.....	349
Vitamin D for neuroprotection in PD	349
Vaccine for PD	349
Clinical trials of neuroprotection in Parkinson's disease	350
Evaluation of neuroprotective therapies for PD	351
Current status and future challenges for neuroprotection in PD	353
8. Neuroprotection in Alzheimer Disease	355
Introduction	355
Pathomechanism of Alzheimer's disease	355
Pathology of AD	355
<i>Cerebral atrophy and neuronal loss</i>	355
Neuritic plaques and neurofibrillary tangles	355
Role of tau in the pathogenesis of AD	356
RNA-binding proteins and AD	356
Amyloid precursor protein	356
<i>APP intracellular domain</i>	357
<i>Relation of APP mutations to CNS disorders.....</i>	357
<i>Relation of APP to Aβ deposits and pathogenesis of AD</i>	358
<i>Role of neprilysin in Aβ degradation</i>	358
<i>Role of secretases in amyloid cascade</i>	359
<i>Role of nicastrin.....</i>	360
Neurotoxicity of A β deposits	360
<i>Aβ production and clearance</i>	360
<i>Aβ-mediated synaptic and cognitive deficits</i>	361
<i>Interaction of Aβ with neuron-specific Na$^{+}$/K$^{+}$-ATPase α3 subunit</i>	361
<i>Relation of Aβ deposits to synaptic activity.....</i>	362
<i>Role of dsDNA breaks in neurodegeneration due to Aβ.....</i>	362
<i>Sequence of events in neurotoxicity of Aβ.....</i>	362
Impairment of mitochondrial energy metabolism	363
Disturbances in brain metabolism in early AD	363
Disturbance of lipid metabolism in the brain	364
Dopamine and AD	364
Functioning role of genes in pathomechanism of AD	364
Insulin, diabetes and AD	365
<i>Mechanisms underlying cognitive deficits in AD.....</i>	366
Microglia and AD.....	366
Neuroinflammation and AD	366
<i>Nitric oxide and AD</i>	367
<i>Oxidative stress and AD.....</i>	369
Spread of neurodegeneration	370
Risk factors in the etiology of AD	371
<i>Epigenetic link between aging and AD</i>	371
<i>Level of education/type of job and risk of AD.....</i>	372
<i>Metals and AD</i>	372
<i>Psychosocial stress and risk of AD.....</i>	373
<i>Sleep deprivation</i>	374
<i>Traumatic brain injury and AD</i>	374
AD and cognitive impairment with aging	375
Concluding remarks on pathophysiology of AD	375
Management of Alzheimer's disease	377
Neuroprotective approaches to Alzheimer's disease	378

Antiapoptotic agents.....	380
Phenserine	380
Antiinflammatory drugs for neuroinflammation.....	380
Etanercept	380
NSAIDS for AD	381
<i>Nitric oxide-donating NSAIDs</i>	382
PPARgamma agonists	382
Antioxidant and free radical scavengers.....	382
Colostrinin	382
Curcumin	383
Dehydroascorbic acid	383
Melatonin.....	383
Resveratrol for AD	384
Antisense approaches to AD	384
Antisense PNA in AD.....	385
Antisense tau in AD.....	385
Cell therapy for AD.....	385
Choroid plexus epithelial cells for AD	385
Stem cell transplantation for AD	386
<i>Autologous adipose tissue derived mesenchymal stem cells</i>	386
<i>Neural stem cells transplantation</i>	386
<i>Neuronal differentiation of implanted NSCs enhanced by drugs</i>	386
<i>NSCs improve cognition in AD via BDNF</i>	387
<i>Potential benefits of grafting NSCs in AD</i>	387
<i>Use of autologous stem cells for dementia</i>	387
Clearance of Aβ deposits and plaques.....	388
Galantamine-induced A β clearance.....	388
Monoclonal antibodies for removal of A β	388
<i>Crenezumab</i>	388
<i>Gantenerumab</i>	388
<i>Solanezumab</i>	389
Nanotechnology for removal of A β deposits	389
Nilotinib	390
Cholesterol lowering agents for AD	390
Statins for reducing the risk of AD.....	390
Gene therapy for Alzheimer disease	390
Rationale	390
NGF gene therapy for AD	391
<i>FGF2 gene transfer in AD</i>	392
<i>Neprilisin gene therapy</i>	392
<i>Viral gene transfer of APPsa for rescuing synaptic failure in AD</i>	393
<i>Gene vaccination</i>	393
<i>Combination of gene therapy with other treatments for AD</i>	393
Glutamate antagonists.....	394
Memantine	394
Inhibition of Aβ formation	395
Chelation of metals	395
<i>Clioquinol</i>	395
<i>Copper chelation</i>	395
<i>Next generation multifunctional chelating agents for AD</i>	396
Secretase modulators.....	396
<i>Neuroprotection by α-secretase cleaved APP</i>	396
<i>Inhibitors of β-secretase</i>	397
<i>Inhibitors of γ-secretase</i>	398
Miscellaneous neuroprotective agents	399
Cerebrolysin	399
Ginkgo biloba	399
Tetrahydrcannabinol for neuroprotection in AD	400
Nanobiotechnology-based therapeutics for AD	401
Nanobody-based drugs for AD	401
Nanoencapsulation for delivery of vitamin E for Alzheimer disease	401
Selegiline-PEG nanoparticles targeting A β fibrils in Alzheimer disease.....	401
Neurotrophic factors for neuroprotection in AD	402
AL-108	402
Brain derived neurotrophic factor	402
Neotrofin (AIT-082).....	402
Small molecule compounds binding to neurotrophin receptor p75NTR.....	403
Limitations of the use of NTFs for AD.....	403
Neuroprotective effect drugs not primarily developed for AD	404
Antiepileptic drugs	404
<i>Lamotrigine</i>	404

<i>Levetiracetam</i>	404
Antimicrobial drugs	404
<i>Dapsone</i>	404
<i>Antimicrobial drugs against Chlamydia pneumoniae</i>	405
<i>Antiviral therapy in AD</i>	405
Antidiabetic drugs	406
<i>Insulin</i>	406
<i>Metformin</i>	406
<i>Rosiglitazone</i>	407
Antihypertensive drugs	407
<i>Angiotensin-converting enzyme inhibitors</i>	407
<i>Angiotensin receptor blockers</i>	407
<i>Bexarotene</i>	408
<i>Dimebon</i>	408
Drugs acting on estrogen receptors	409
<i>Estrogen</i>	409
<i>Raloxifene</i>	410
<i>Granulocyte-macrophage colony-stimulating factor</i>	410
Inhibitors of neuroinflammation	410
<i>Ceramide</i>	410
<i>CSP-1103</i>	410
<i>Fingolimod</i>	411
<i>Interferon beta-1a</i>	411
<i>Lithium</i>	411
MAO-B inhibitors	412
<i>Ladostigil tartrate</i>	412
<i>Methylene blue</i>	412
Phosphodiesterase inhibitors as neuroprotectives.....	412
<i>Rapamycin</i>	413
<i>Saracatinib</i>	413
<i>Testosterone</i>	413
<i>Valproic acid</i>	414
Restoration of factors deficient in the aging brain	414
Reversal of cognitive impairment in aging by activation of creb protein.....	414
Reversal of cognitive impairment in aging by GDF11 protein	415
Restoration of repressor element 1-silencing transcription factor.....	415
Vaccines for AD	415
Active immunization with A β	416
Passive immunization with Mabs.....	416
Other vaccines for AD.....	417
Mechanism of reduction of A β plaque pathology by immunization.....	417
Perspectives on vaccines for AD	418
Vitamins	418
Vitamin E as antioxidant	418
Vitamin B for lowering homocysteine	418
Folic acid	419
Combined therapeutic approaches to AD	419
Clinical trials in AD	419
Concluding remarks on clinical trials of AD	428
Future prospects of neuroprotection in AD	429
Mild cognitive impairment	429
Relation of MCI to AD	430
Neuroprotection in MCI	430
<i>Pharmacological approaches for MCI</i>	430
<i>Non-pharmacological approaches to MCI and AD</i>	432
9. Neuroprotection in Huntington Disease	433
Introduction	433
Pathophysiology of HD	433
Management of Huntington's disease	435
Neuroprotection in Huntington's disease	435
Antipsychotic D ₂ and 5-HT _{1A} antagonists	436
Caspase inhibitors.....	436
Cysteine and neuroprotection in HD	437
<i>Cysteine metabolism reprogramming for neuroprotection in HD</i>	437
<i>Cysteamine</i>	437
Drugs that block inappropriate calcium release from neurons	437
Enhancing protease activity for clearance of mHtt.....	437
Eicosapentaenoic acid.....	438
Fingolimod	438
Free radical scavengers	438

Histone deacetylase inhibitors	439
Phosphodiesterase inhibitors	439
Polyglutamine aggregation inhibitors	439
Pramipexole	440
Pridopidine	440
RRAS signaling pathway inhibition	440
Simvastatin as a neuroprotective in HD	440
Single chain Fv antibodies	441
SIRT1 activators for neuroprotection in HD	441
SIRT2 inhibitors for neuroprotection in HD	441
Synaptic activation of NMDA receptors	442
Targeting mutant huntingtin protein	442
Tetrabenazine	443
Combinatorial therapy and targeting multiple pathways in HD	443
Cell therapy for HD	443
<i>Cell transplants for HD</i>	444
<i>Stem cell-based therapy for HD</i>	444
Neurotrophic factors and gene therapy	445
Antisense therapeutics for Huntington's disease	445
<i>HTT_{RX}/RG6042 for HD</i>	445
RNAi-based therapies for Huntington's disease	446
10. Neuroprotection in Amyotrophic Lateral Sclerosis	447
Introduction	447
Pathophysiology of ALS	447
Neuroprotective therapies for ALS	452
Activated protein C	453
AIMSPRO	453
Anakinra	454
Antisense therapy	454
Arimoclomol for ALS	454
Ceftriaxone for ALS	455
Coenzyme Q10 for ALS	455
COX-2 inhibitors for ALS	455
Dexpramipexole	455
Diallyl trisulfide	456
Edaravone for ALS	456
Erythropoietin for ALS	456
Gene therapy for ALS	457
<i>Gene editing for ALS</i>	457
Glatiramer acetate	458
GM604	458
Insulin-like growth factor	458
Ketogenic diet for neuroprotection in ALS	459
Lenalidomide	459
Lithium for neuroprotection in ALS	459
Masitinib	460
Melatonin for ALS	460
Methylcobalamin	460
Olesoxime as neuroprotective for ALS	461
ONO-2506	461
Riluzole	461
RNAi-based therapy for ALS	462
Sodium phenylbutyrate	462
Stem cell therapy	462
<i>Clinical applications</i>	462
<i>Stem cell-based drug discovery for ALS</i>	463
<i>Suppressors of mTDP-43 toxicity</i>	464
Talampbane	464
Tamoxifen	464
Vaccination for ALS caused by SOD1 mutations	465
Vascular endothelial growth factor for ALS	465
Vitamin E for ALS	465
Clinical trials of neuroprotective therapies for ALS	465
Concluding remarks and future prospects	466
Multi-omics approach to ALS	466
Use of CRISPR/Cas9 technology to find new targets in ALS	467
Concluding remarks on neuroprotection in ALS	467
11. Neuroprotection in Miscellaneous Neurological Disorders	469
Introduction	469

Neuroprotection in synaptopathies	469
Neuroprotection in ASD	470
Neuroprotection in fragile X syndrome	470
Neuroprotection in dementia	470
Age-related dementia	470
<i>Aging brain and oxidative stress</i>	471
<i>Hsp70 and age-related neurodegeneration.....</i>	471
<i>Pharmacological approaches for treatment of age-related dementia</i>	472
<i>Mental training to prevent decline of mental function with aging</i>	472
<i>Physical exercise to prevent decline of mental function with aging.....</i>	473
<i>Concluding remarks on neuroprotection of the aging brain</i>	474
Vascular dementia	474
<i>Prediction of dementia in persons with vascular risk factors.....</i>	474
<i>Management of subcortical vascular dementia</i>	475
Neuroprotection in Lewy body dementia	476
Neuroprotection in AIDS dementia	476
Multiple system atrophy	477
Epilepsy	477
Mechanisms of neuronal damage in epilepsy	478
Strategies for neuroprotection in epilepsy	478
AEDs and neuroprotection.....	479
Cell therapy for neuroprotection in epilepsy.....	480
<i>Cell therapy of posttraumatic epilepsy</i>	481
<i>Cell therapy for temporal lobe epilepsy</i>	481
<i>Cell therapy for pharmacoresistant epilepsies</i>	481
Drugs targeting mossy cells in drug-resistant epilepsy.....	482
Gene therapy for neuroprotection in epilepsy	482
Hyaluronan-based preservation of brain ECS volume.....	483
Hypothermia for neuroprotection in status epilepticus.....	483
Ketogenic diet for prevention of seizures.....	483
miR-211 as an attenuator of cholinergic-mediated seizures.....	484
Multiple sclerosis	484
Introduction	484
Epidemiology of multiple sclerosis	484
Pathophysiology	485
Current management of multiple sclerosis.....	485
Specific therapies for MS based on pathomechanism	486
Neuroprotection in multiple sclerosis	486
Clinical trials of neuroprotective therapies for MS.....	488
Neuroprotection by control of progressive forms of multiple sclerosis	489
Neuroprotection by controlling autoimmune inflammation in the brain	490
Neuroprotection by sealing the BBB with imatinib	490
TRPM4 cation channel blockers	491
Remyelination for neuroprotection in multiple sclerosis	491
Agents for neuroprotection in multiple sclerosis	491
<i>Angiotensin-II inhibitors</i>	491
<i>Antiglutamate agents</i>	492
<i>Antioxidants for neuroprotection in MS</i>	492
<i>Antisense and RNAi approaches to MS</i>	492
<i>B cell depletion therapy</i>	493
<i>Cell therapy for multiple sclerosis.....</i>	493
<i>Cannabinoids for neuroprotection in MS</i>	495
<i>Cladribine</i>	496
<i>Curcumin as a neuroprotectant in multiple sclerosis</i>	496
<i>Cytokine-directed therapies in MS.....</i>	497
<i>Dalfampridine in MS</i>	497
<i>Dimethyl fumarate and diroximel fumarate</i>	497
<i>DNA vaccine for MS.....</i>	498
<i>Erythropoietin as a neuroprotective in MS</i>	498
<i>Evobrutinib</i>	498
<i>Fingolimod</i>	499
<i>Fusokine composed of GM-CSF and IL-15 for immune suppression.....</i>	499
<i>Gene therapy for MS</i>	500
<i>Hookworm treatment for relapsing MS.....</i>	500
<i>Ibudilast for MS</i>	501
<i>Interferons.....</i>	501
<i>Iron chelators.....</i>	501
<i>IVIG for MS.....</i>	502
<i>Kinase inhibitors</i>	502
<i>Laquinimod</i>	502
<i>Melatonin for MS.....</i>	502

<i>Minocycline for MS</i>	503
<i>Monoclonal antibodies for MS</i>	503
<i>Natalizumab</i>	504
<i>Natural human antibodies for repair of myelin</i>	505
<i>Neurotrophic factors for multiple sclerosis</i>	505
<i>Nimodipine</i>	506
<i>Oral immunomodulatory agents for MS</i>	506
<i>Protein kinase Cβ as a therapeutic target for stabilizing BBB in MS</i>	506
<i>Recombinant T-cell ligands</i>	507
<i>Siponimod</i>	507
<i>Statins for MS</i>	507
<i>Teriflunomide</i>	508
<i>Tolerance-directed immunotherapy for MS</i>	508
<i>Ursolic acid</i>	509
Concluding remarks and future prospects for neuroprotection in MS	509
Neuroprotection in anti-NMDA receptor encephalitis	510
Neuroprotection in transverse myelitis	510
Neuroprotection in decompression sickness	510
Neuroprotection in victims of drowning	511
Neuroprotection in CSF circulatory disorders	511
Neuroprotection in hydrocephalus	512
Neuroprotection in normal pressure hydrocephalus	512
Neuroprotection in cerebral edema	513
Pathomechanism and types of cerebral edema	513
Causes of cerebral edema	514
Principles of management of cerebral edema	514
Guidelines for management of acute cerebral edema	515
Neuroprotection in infections of the CNS	516
Neuroprotection in bacterial meningitis	516
<i>Mechanism of neural injury in bacterial meningitis</i>	516
<i>Strategies for neuroprotection</i>	517
Neuroprotection in progressive multifocal leukoencephalopathy	517
Neuroprotection in cryptococcal meningitis	517
Neuroprotective approach to rabies	518
Neuroprotection in cerebral malaria	519
Neuroprotection in neuroinflammation	519
Role of antiinflammatory drugs in the management of neuroinflammation	520
<i>Nanoparticles for targeted delivery of antiinflammatory drugs</i>	520
Personalized management of neuroinflammation	521
Neuroprotection in complications of systemic disorders	521
Neurological complications of cardiovascular disorders	521
<i>Neuroprotection after myocardial infarction</i>	521
<i>Neuroprotection in hypertensive encephalopathy</i>	522
<i>Management of hypertension to prevent dementia</i>	522
Neuroprotection in complications of diabetes	523
<i>Neuroprotection in hypoglycemic coma</i>	523
<i>Neuroprotection in diabetic ketoacidosis</i>	524
<i>Neuroprotection in diabetic retinopathy</i>	524
Neurological complications of liver disorders	525
<i>Hepatic encephalopathy</i>	525
<i>Bilirubin encephalopathy</i>	526
Neuroprotection in neurological complications of renal disease	527
Neuroprotection in fever	527
<i>Pharmacologic approaches for fever</i>	529
<i>Cooling the brain for neuroprotection</i>	529
Neuroprotection in toxic encephalopathies	530
Encephalopathy due to organophosphorus poisoning	530
<i>Sarin gas</i>	530
Neuroprotection against chemotherapy-induced brain damage	531
Neuroprotection against alcohol	532
<i>Alcoholic neurologic disorders</i>	532
<i>Fetal alcohol syndrome</i>	532
<i>Pathogenesis of alcohol-induced damage to the nervous system</i>	532
<i>Neuroprotection against neurotoxicity of alcohol</i>	533
Neuroprotection against exposure to therapeutic radiation	533
Neuroprotection against radiation encephalopathy	533
Role of SOD in protection against radiation-induced hippocampal dysfunction	534
Catalase reduces mitochondrial ROS for neuroprotection from proton irradiation	534
Neuroprotection of the fetus and the neonate	534
Neuroprotection in preterm babies	535
Neuroprotection in neonatal hypoxic-ischemic brain injury	535

<i>Pathomechanism of neonatal hypoxic-ischemic brain injury</i>	535
<i>Management of neonatal hypoxia-ischemia</i>	536
<i>Approaches to neuroprotection in neonatal hypoxia-ischemia</i>	536
<i>Hyperbaric oxygen for neonatal hypoxia-ischemia</i>	537
<i>Hypothermia for neonatal hypoxia-ischemia</i>	537
<i>Melatonin for neonatal hypoxia-ischemia</i>	537
<i>Minocycline for neonatal hypoxia-ischemia</i>	537
<i>Nicotinamide mononucleotide adenylyl transferase 1</i>	538
<i>Nitric oxide inhalation for neonatal hypoxia-ischemia</i>	538
<i>Plasminogen activator inhibitor-1 for neonatal hypoxia-ischemia</i>	538
<i>Recombinant erythropoietin for neonatal hypoxia-ischemia</i>	538
Neuroprotection in carbon monoxide poisoning	539
Pathomechanism of CO poisoning as a basis for neuroprotection.....	539
Management of CO poisoning	540
Neuroprotection after cardiac arrest	540
Neuroprotection in delayed post-hypoxic leukoencephalopathy	541
Neuroprotection in sleep apnea	541
Neuroprotection in mitochondrial dysfunction	542
Mitochondrial permeability transition	542
Mitochondrial approaches for neuroprotection.....	543
Methylene blue	544
Mitochondrial encephalopathies	544
<i>Neuroprotection in mitochondrial encephalopathies</i>	545
Neuroprotection in psychiatric disorders	545
Electroconvulsive therapy and neuroprotection	545
Neuroprotection in schizophrenia	545
<i>Cognitive impairment in schizophrenia</i>	546
Neuroprotection in stress-induced neuropsychiatric disorders	546
<i>Adenosine A_{2A} receptor antagonists for neuroprotection in stress</i>	546
<i>Role of neurotrophic factors in stress-induced psychiatric disorders</i>	547
<i>Stress and dementia</i>	547
Neuroprotection in hearing loss	547
Causes of hearing loss	548
Pathomechanism of hearing loss	548
Prevention and treatment of hearing loss	549
<i>Hyperbaric oxygen for hearing loss</i>	549
<i>Stem cell therapy for sensory hearing loss</i>	549
<i>Gene therapy for sensorineural hearing loss</i>	550
<i>Pharmaceutical approaches to hearing loss</i>	551
<i>Prevention of drug-induced hearing loss</i>	552
Neuroprotection of peripheral nerves	552
Neuroprotective agents for peripheral nerves	552
<i>Acetyl-L-carnitine for peripheral nerve injuries</i>	553
<i>Atorvastatin for peripheral nerve injuries</i>	553
<i>Erythropoietin for neuroprotection in peripheral nerve injuries</i>	553
Neuroprotection in peripheral nerve injuries	554
<i>Role of hyperbaric oxygen in peripheral nerve injuries</i>	554
<i>Role of neurotrophic factors in peripheral nerve injuries</i>	554
<i>Pharmacological approaches to Schwann cells</i>	554
<i>Role of gene therapy in neuroprotection of injured peripheral nerves</i>	555
<i>Schwann cell transplantation for peripheral nerve injury</i>	555
<i>Targeting Wallerian degeneration slow protein for neuroprotection</i>	555
Peripheral neuropathy	556
<i>Neuroprotection in diabetic neuropathy</i>	556
<i>Cell therapy for neuroprotection in diabetic neuropathy</i>	556
<i>Gene therapy in diabetic neuropathy</i>	556
<i>Neuroprotection in chemotherapy-induced neuropathy</i>	557
Neuroprotection in chronic inflammatory demyelinating polyradiculoneuropathy	558
Neuroprotection in Charcot-Marie-Tooth disease 1A	558
12. Neuroprotection of the Optic nerve and the Retina	559
Introduction	559
Optic neuropathy	559
Pathophysiology	559
Neuroprotection in optic neuritis	560
<i>Azathioprine</i>	561
<i>Flupirtine</i>	562
<i>Eculizumab for neuromyelitis optica</i>	562
<i>Sodium channel blockers</i>	562
<i>Resveratrol</i>	563
<i>Satralizumab</i>	563

Neuroprotection in optic nerve trauma	563
Potential regeneration of the optic nerve.....	563
Neuroprotection of optic nerve in glaucoma	564
Aminoguanidine as a neuroprotective in glaucoma	565
Antiglutamate agents for neuroprotection of optic nerve	565
Betaxolol	565
NGF eye drops	566
Targeting A β in glaucoma treatment.....	566
TNF- α blockers for neuroprotection in glaucoma	566
Concluding remarks about neuroprotection in glaucoma.....	567
Neuroprotection in retinal ischemia.....	567
β -adrenoceptor antagonists.....	567
Brimonidine as a neuroprotective in ischemic retinopathy.....	568
Endogenous neuroprotection in the retina	568
Erythropoietin for neuroprotection of retinal ischemia	568
Gene therapy for retinal neuroprotection.....	569
Hyperbaric oxygen for central retinal artery occlusion.....	569
Levodopa for treating non-arteritic anterior ischemic optic neuropathy	569
Thioredoxin as a neuroprotective agent in retinal ischemia.....	569
Protection against oxygen-induced retinopathy	570
Neuroprotection in macular degeneration	570
Epidemiology.....	570
Pathomechanism of AMD	570
Current treatment of AMD.....	571
Novel neuroprotective strategies against retinal degeneration	572
Antiangiogenic agents	573
Humanized MAb against A β	573
LXR agonists	574
Neurotrophic factors for neuroprotection in AMD	574
<i>CNTF for neuroprotection in AMD</i>	574
<i>N-acetylserotonin derivatives</i>	574
Nutritional protection against AMD	574
Progestogenic hormones.....	575
Protection of retinal cells from oxidative-stress-induced apoptosis.....	575
Sulindac	575
Tandospirone	576
Cell therapy for macular degeneration	576
<i>Retinal pigment epithelial cells.....</i>	576
<i>Stem cell transplantation in the retina</i>	576
<i>Neural progenitor cells.....</i>	577
<i>hESC-derived RPE cells for AMD.....</i>	577
Gene therapy for retinal degeneration	578
<i>Combining stem cell and gene therapies for retinal disorders.....</i>	579
RNAi-based treatments for AMD	579
Neuroprotection in proliferative diabetic retinopathy	580
RNAi-based approaches to diabetic retinopathy.....	580
Clinical trials for optic nerve and retinal neuroprotection	580
13. Neuroprotection during Anesthesia and Surgery	583
Introduction	583
Anesthetic agents as neuroprotectives	583
Barbiturates	583
<i>Thiopental.....</i>	584
Etomidate	585
Propofol	585
Ketamine	585
Gaseous anesthetics.....	586
<i>Isoflurane</i>	586
<i>Xenon.....</i>	586
Local anesthetics	587
Monitoring of CNS function during anesthesia and surgery	587
Monitoring of cerebral function	587
Monitoring of spinal cord function during spinal surgery	587
Perioperative neuroprotection	588
Neuroprotection during cardiovascular procedures	589
CNS complications of cardiac surgery	589
Neuroprotective strategies during cardiac surgery	590
<i>Neuroprotection before anticipated or induced cardiac arrest.....</i>	591
<i>Neuroprotection during coronary artery bypass grafting.....</i>	591
<i>Preconditioning with hyperbaric oxygen.....</i>	592
<i>Neuroprotection in aortic surgery.....</i>	593

<i>Pharmacologic strategies for neuroprotection in aortic surgery</i>	593
Cerebral protection during organ transplantation surgery	594
Cerebral protection in neurosurgery	594
Cerebral angiography and endovascular surgery	594
Cerebral protection during surgery for arteriovenous malformations	594
Cerebral protection during surgery of intracranial aneurysms	594
Management of subarachnoid hemorrhage	595
<i>Vasospasm associated with subarachnoid hemorrhage</i>	595
Cerebral protection during carotid endarterectomy.....	598
Cerebral protection during surgery of brain tumors	598
Neuroprotective measures prior to surgery.....	599
<i>HBO preconditioning for neuroprotection during surgery</i>	599
Neuroprotection following surgery.....	599
<i>Neuroprotection by cranioplasty after decompressive craniectomy</i>	600

Tables

Table 1-1: Historical landmarks in the development of neuroprotection	35
Table 1-2: Intrinsic neuroprotective factors.....	40
Table 1-3: Common features of pathophysiology of brain damage in diseases	48
Table 1-4: Place of neuroprotection in management of CNS disorders	56
Table 1-5: Indications for the use of neuroprotection	56
Table 1-6: Neuroprotective nanoparticles.....	63
Table 2-1: A classification of neuroprotective agents	67
Table 2-2: The neuroprotective effect of antiepileptic drugs	77
Table 2-3: Neuroprotective affect of minocycline in animal models.....	81
Table 2-4: Classification of antioxidants or free radical scavengers with neuroprotective potential.....	89
Table 2-5: Role of erythropoietin in the nervous system	95
Table 2-6: Ionotropic glutamate receptors	101
Table 2-7: Classification of metabotropic glutamate receptors (mGluRs).....	101
Table 2-8: Methods for neuroprotection based on nonpharmacological preconditioning	152
Table 3-1: Cerebrovascular diseases that are relevant to neuroprotection	155
Table 3-2: Neuroprotective strategies for stroke	167
Table 3-3: Selected effective combinations of hypothermia with other neuroprotective strategies for the treatment of ischemic stroke in experimental models	201
Table 3-4: Neuroprotective gene transfer in models of cerebral ischemia	209
Table 3-5: Neuroprotective gene therapy in animal stroke models	210
Table 3-6: Neuroprotective agents in clinical development for acute cerebrovascular disease	212
Table 3-7: Some failed trials for neuroprotective therapy for stroke	215
Table 3-8: Preclinical assessment of neuroprotective agents in acute stroke models.....	224
Table 3-9: Stroke prevention based on control of risk factors	226
Table 4-1: Classification of closed TBI	229
Table 4-2: Pathophysiologic responses to TBI and for neuroprotective strategies	231
Table 4-3: Current conventional management of traumatic brain injury	239
Table 4-4: Neuroprotective strategies for traumatic brain injury	242
Table 4-5: Intrinsic factors that influence regeneration in the central nervous system	262
Table 4-6: A classification of approaches to regeneration of the brain following injury	262
Table 4-7: Ongoing or completed clinical trials for neuroprotection in TBI	264
Table 4-8: Discontinued or failed clinical trials for neuroprotection in TBI.....	265
Table 5-1: Secondary mechanisms in spinal cord injury	270
Table 5-2: Neuroprotective and regenerative approaches for SCI.....	272
Table 5-3: Clinical trials for neuroprotection in SCI	287
Table 6-1: Neurodegenerative disorders with dementia	298
Table 6-2: Drugs in clinical trials for spinal muscular atrophy	305
Table 6-3: Pharmacological approaches to neuroprotection in CJD	307
Table 6-4: Glutamate-based therapies in clinical development for neurodegenerative disorders.....	309
Table 7-1: Prevalence of Parkinson's disease in major markets 2019-2029	313
Table 7-2: Factors in the etiology of Parkinson's disease.....	313
Table 7-3: Strategies for the treatment of Parkinson's disease	322
Table 7-4: Gene therapy techniques applicable to Parkinson disease	337
Table 7-5: Current clinical trials of neuroprotective therapies for Parkinson disease	350
Table 7-6: Failed clinical trials of neuroprotective therapies for Parkinson disease.....	350
Table 7-7: Evaluation of neuroprotective agents for PD	352
Table 8-1: Relation of mutations in amyloid precursor protein to CNS disorders.....	357
Table 8-2: Risk factors for Alzheimer's disease	371
Table 8-3: Cholinergic approaches to the treatment of Alzheimer's disease	377
Table 8-4: Neuroprotective approaches to Alzheimer's disease	378
Table 8-5: Clinical trials in Alzheimer disease	419
Table 8-6: Discontinued, failed or inconclusive clinical trials of Alzheimer disease	425
Table 8-7: Strategies for discovery of neuroprotective therapies for AD	429

Table 9-1: Neuroprotective approaches in HD.....	435
Table 10-1: Hypotheses for the pathogenesis of amyotrophic lateral sclerosis	447
Table 10-2: Genetic diagnostic biomarkers of ALS.....	450
Table 10-3: Classification of neuroprotective agents for amyotrophic lateral sclerosis	452
Table 11-1: Therapeutic approaches to subcortical vascular dementia	475
Table 11-2: Measures for neuroprotection against the sequelae of seizures.....	479
Table 11-3: Neuroprotective effect of AEDs in animal models of status epilepticus (SE)	480
Table 11-4: Specific therapies for MS based on postulated pathomechanisms.....	486
Table 11-5: Approved neuroprotective/neuromodulating therapies for multiple sclerosis.....	487
Table 11-6: Neuroprotective therapies for multiple sclerosis in clinical trials	488
Table 11-7: Causes of cerebral edema.....	514
Table 11-8: Principles of management of cerebral edema	514
Table 11-9: Methods for management of neuroinflammation	520
Table 11-10: Measures to prevent acute bilirubin encephalopathy.....	526
Table 11-11: Fever associated with neurologic disorders.....	528
Table 11-12: Approaches to neuroprotection in neonatal hypoxia-ischemia	536
Table 11-13: Drugs with neuroprotective effect at mitochondrial level	543
Table 11-14: Causes of sensorineural hearing impairment	548
Table 11-15: Strategies for prevention and treatment of sensorineural hearing loss	549
Table 11-16: Agents for neuroprotection of the peripheral nervous system	553
Table 11-17: Neuroprotective agents for chemotherapy-induced peripheral neuropathy	557
Table 12-1: Causes of optic neuropathy.....	559
Table 12-2: Clinical trials of neuroprotective therapies in optic neuritis	561
Table 12-3: Neuroprotection of the optic nerve in glaucoma.....	564
Table 12-4: Strategies for neuroprotection in retinal ischemia	567
Table 12-5: Novel neuroprotective strategies against retinal degeneration	572
Table 12-6: Clinical trials for retinal neuroprotection	581
Table 13-1: CNS complications associated with cardiac procedures	589
Table 13-2: Strategies for protection of the brain during cardiac surgery	590
Table 13-3: Medical and surgical methods of cerebral vasospasm management.....	596
Table 13-4: Neuroprotection by prevention of vasospasm	596

Figures

Figure 1-1: A three-stage model of ischemic hypoxic disturbances of the brain.....	52
Figure 2-1: Mechanism of neuroprotective effect of sigma-1 receptor agonists	75
Figure 2-2: NMDA receptor ion channel complex.....	105
Figure 2-3: Neuroprotective effect of galantamine	126
Figure 3-1: Some steps in the ischemic cascade and site of action of neuroprotectives	156
Figure 3-2: Relationship between dementia and acute ischemic stroke	166
Figure 3-3: Pathomechanism of ischemic stroke and neuroprotective strategies	168
Figure 3-4: Molecules involved in preconditioning for neuroprotection in ischemia.....	203
Figure 3-5: A roadmap for neuroprotection	225
Figure 4-1: Cascade of events following traumatic brain injury	231
Figure 4-2: Neurometabolic cascade of mild TBI	233
Figure 4-3: Secondary injury mechanisms after TBI	234
Figure 4-4: Management of raised ICP after TBI	240
Figure 5-1: Pathomechanism of acute spinal cord injury	270
Figure 6-1: Identification of protein targets in neurodegenerative disorders	312
Figure 7-1: Neuroprotective strategies against death of dopamine-containing neurons in PD	319
Figure 8-1: Mechanisms of A β clearance	361
Figure 8-2: Nitric oxide neurotoxicity and neuroprotection in relation to Alzheimer disease	368
Figure 8-3: Oxidative stress and Alzheimer disease.....	370
Figure 8-4: Pathomechanism of AD	377
Figure 9-1: Role of HTT protein in pathogenesis of HD and points of intervention.....	443
Figure 11-1: A schematic overview of synaptopathies.....	469
Figure 11-2: Common mechanisms of neural damage in cerebral ischemia and seizures	478
Figure 11-3: Role of neuroprotection in epilepsy and its treatment.....	479
Figure 11-4: Mechanisms of neonatal hypoxia-ischemia and targets for neuroprotection.....	536