

TABLE OF CONTENTS

0. Executive Summary	25
1. Introduction	28
Definitions	28
Historical development of neuroprotection	28
Intrinsic neuroprotective factors	29
Neuroprotective gene expression	30
<i>Upregulation of GADD34</i>	<i>30</i>
<i>Induction of NR4A proteins by CREB in neurons</i>	<i>31</i>
Neurotrophic factors	31
Intrinsic nonenzymatic antioxidants	31
Activation of transcription factor Nrf2	32
Intrinsic neuroprotective proteins	32
<i>aB-crystallin</i>	<i>32</i>
<i>Excitatory amino acid transporters</i>	<i>32</i>
<i>Extracellular serine protease thrombin</i>	<i>32</i>
<i>Galanin</i>	<i>33</i>
<i>Neuroglobin</i>	<i>33</i>
<i>Nuclear factor I-A</i>	<i>33</i>
<i>Prion protein</i>	<i>34</i>
<i>Rai adaptor protein</i>	<i>34</i>
Stem cell factor	34
Role of the immune system in neuroprotection	35
Induction of DNA repair enzymes for neuroprotection	35
Pathomechanisms of CNS injury as basis for neuroprotection	36
Biomarkers of neurological disorders and neuroprotection	36
CNS biomarker identification using proteomics	36
Brain imaging for detection of biomarkers	37
Role of neuroprotection in various neurological disorders	37
Neuroprotection and neuroregeneration	38
Acute versus chronic neuroprotection	38
Discovery and evaluation of neuroprotective agents	39
Neuroprotective drug discovery	39
Discovery of CNS drugs that penetrate the blood-brain barrier	40
In vitro assays for the evaluation of neuroprotective agents	40
Oxidative injury model to test neuroprotective drugs	40
Apoptosis model for designing neuroprotective drugs	41
Transgenic mouse models of neurological disorders	41
Evaluating effects of neuroprotective drugs on living brain slices	41
Role of brain imaging in neuroprotective drug discovery and development	42
<i>Positron emission tomography</i>	<i>42</i>
<i>Role of single photon emission computed tomography</i>	<i>42</i>
<i>Functional CT scanning to evaluate cerebrovascular protection</i>	<i>43</i>
<i>Magnetic resonance imaging for the evaluation of neuroprotectives</i>	<i>43</i>
Application of nanotechnology to neuroprotection	44
Evaluation criteria for potential neuroprotective agents	44
2. Neuroprotective Agents	45
Classification of neuroprotective agents	45
Activated protein C	49
Activity-dependent neuroprotective protein	49
Adenosine analogs	50
Propentofylline	50
Antidepressants	51
Antidepressant-induced neurogenesis	51
Neurogenesis induced by electroconvulsive therapy	51
Neuroprotective effect of selective serotonin reuptake inhibitors	51
Antiepileptic drugs as neuroprotectives	53
Phenytoin	54
Valproic acid	54
Levetiracetam	54
Antiinflammatory agents	55
Aspirin	55
Interleukin-1 antagonists	55
COX-2 inhibitors	56
<i>Nimesulide</i>	<i>56</i>
Gold microparticles as anti-neuroinflammatory agents	56

Minocycline	57
Anti-apoptosis agents	58
Activated protein C.....	58
Calpain inhibitors	59
Caspase inhibitors	59
DNA binding drugs	59
Lithium	59
Olesoxime	60
Omega-3 fatty acids.....	60
<i>Docosahexaenoic acid</i>	60
Poly(ADP-ribose) polymerase inhibitors.....	61
Prevention of apoptosis by binding of proNGF to sortilin.....	61
Antioxidants/free radical scavengers	62
Free radical generation	62
Natural defenses against oxidative stress	62
Effects of oxidative damage.....	62
<i>Oxidative damage and aging</i>	62
<i>Neuronal damage by free radicals</i>	63
<i>Oxidative damage and neurodegenerative disorders</i>	63
Measures to control oxidative stress	64
<i>Categories of therapeutic antioxidants</i>	64
<i>Alpha-phenyl-tert-butyl nitron</i>	64
<i>Coenzyme Q10</i>	65
<i>Dihydroergocryptine</i>	65
<i>Flavonoids</i>	66
<i>Mitochondria-targeted antioxidants</i>	66
<i>Nanoparticles as neuroprotective antioxidants</i>	66
<i>Neuroleptics as antioxidants</i>	67
<i>Nitrones</i>	67
Translation of antioxidant neuroprotection from preclinical to clinical	68
Carbon monoxide and heme oxygenase	68
Cell transplants.....	68
Cells secreting neuroprotective substances.....	68
Stem cells.....	69
Stem cell activation for neuroprotection/regeneration by glucocorticoids	69
Cytokines	69
Erythropoietin.....	69
<i>Non-erythropoietic EPO variants and mimics</i>	71
Granulocyte colony-stimulating factor	72
Delta-opioid receptor agonists	72
FK960	72
Gene therapy	73
Glucagon-like peptide	74
Glatiramer acetate	74
Glutamate antagonists.....	74
Neuroprotection by scavenging blood glutamate	75
N-acylethanolamines for protection against glutamatergic excitotoxicity	76
Glutamate transporters.....	76
Glutamate transporter-mediated neuroprotective effect of drugs.....	76
Neuroprotection by targeting KAI subunit of kainate receptor	77
Glycine-proline-glutamate analogs	77
Herbal preparations	77
Flavonoid wogonin	78
Ginseng	78
Hydrogen sulfide.....	78
NMDA receptor ion channel complex.....	79
NMDA receptor antagonists	80
<i>NMDA NR2B subunit receptor antagonists</i>	80
<i>Ifenprodil</i>	80
<i>Memantine as a neuroprotective agent</i>	80
<i>Magnesium</i>	81
<i>NAALADase inhibitors</i>	81
<i>Gacyclidine</i>	81
<i>N-alkylglycines</i>	81
AMPA receptor modulators	82
Metabotropic glutamate receptor modulators.....	82
Cannabinoids.....	83
Dexanabinol	83
Glutathione	84
Heat shock proteins	84
Hormones	85

Estrogen and neuroprotection.....	85
<i>Neuroprotective effect of estrogen receptor ligands</i>	85
<i>Selective estrogen receptor modulators</i>	86
<i>Mitochondrial mechanisms of estrogen neuroprotection</i>	86
Insulin.....	87
Ion Channel modulators.....	87
Calcium channel blockers.....	87
<i>Ziconotide</i>	88
Na ⁺ channel blockers.....	88
Neuroprotective potassium channel inhibitors.....	89
Kynurenine inhibitors.....	89
Leukocyte adhesion inhibitors.....	89
Modafinil.....	90
Neural regeneration protein.....	90
Neurite outgrowth-promoting prostaglandin compounds.....	91
Neuroimmunophilins.....	91
Cyclosporin-A.....	91
FK506.....	92
Rapamycin.....	92
Neurotrophic factors.....	93
Activity-dependent neurotrophic factor.....	93
Bone morphogenetic proteins.....	93
Brain-derived neurotrophic factor.....	94
Ciliary neurotrophic factor.....	94
Fibroblast growth factors.....	95
Glial cell line-derived neurotrophic factor.....	95
Insulin-like growth factor.....	96
Nerve growth factor.....	96
Neurotrophins.....	97
Osteogenic protein-1.....	97
Pigment epithelium-derived factor.....	97
Transforming growth factor- β 1.....	98
Vascular endothelial growth factor.....	98
Neurotrophic factor-related neuroprotective agents.....	98
<i>Amitriptyline as a TrkA and TrkB receptor agonist</i>	98
<i>Colivelin</i>	98
<i>Gambogic amide</i>	99
<i>Inosine</i>	99
<i>Meteorin</i>	99
<i>Oxygen-regulated protein 150 kD</i>	100
<i>Prosaptide</i>	100
<i>Siagoside</i>	100
<i>Small molecule activators of the Trk receptors</i>	100
Nicotine and nicotinic receptor agonists.....	101
<i>Neuroprotective effect of galantamine mediated via α7nAChRs</i>	101
<i>Galantamine-induced Aβ clearance via α7nAChRs</i>	102
Nitric oxide-based neuroprotection.....	102
Nitric oxide synthase inhibitors.....	102
Nitric oxide mimetics.....	103
Nootropics.....	103
<i>Piracetam</i>	104
Nutraceuticals and food constituents.....	104
Coffee.....	104
Creatine.....	105
Curcumin/curry.....	105
<i>Curcumin as a neuroprotectant in Alzheimer disease</i>	105
<i>Curcumin as a neuroprotectant in stroke</i>	105
<i>Curcumin as a neuroprotectant in multiple sclerosis</i>	106
<i>Mechanism of neuroprotective effect of curcumin</i>	106
Glyceroltriacetate.....	106
Green tea.....	106
Nicotinamide.....	107
Resveratrol.....	107
Osmotic diuretics.....	108
Mannitol.....	108
Osteopontin.....	108
Oxygen therapeutics.....	109
Oxygen carriers.....	109
Hemoglobin-based oxygen carriers.....	109
Perfluorocarbons as oxygen carriers.....	110
Hyperbaric oxygen therapy.....	111

Peptides.....	111
C3-derived peptide for neuroprotection and neuroregeneration	111
Corticotropin-releasing hormone	111
Thyrotropin-releasing hormone	112
Vasoactive intestinal peptide	112
Pharmacological preconditioning	113
PPARs as drug targets for neuroprotection	113
Riluzole.....	113
Role of RNA interference in neuroprotection.....	114
Sigma receptor agonists as neuroprotective agents	114
SIRT group of proteins.....	114
Statins	115
Steroids	116
Dehydroepiandrosterone	116
HF0220.....	117
Sulforaphane	117
Tauroursodeoxycholic acid.....	117
Tetanus toxin as a neuroprotective agent	118
Thrombolytic agents as neuroprotective agents	118
Uncoupling protein 2.....	118
Vaccines as neuroprotectives.....	119
Vitamins as neuroprotective agents.....	119
Vitamin B12	119
Vitamin D.....	120
Non-pharmacological approaches to neuroprotection	120
Environmental enrichment	120
Mental training	120
Physical exercise.....	120
Hypothermia	121
<i>Limitations of hypothermia</i>	<i>121</i>
<i>Hypothermic neuroprotection in hypoxia-ischemia.....</i>	<i>122</i>
Hibernation induced by hydrogen sulfide.....	122
Ketogenic diet	122
Nonpharmacological preconditioning for neuroprotection.....	123
Transcranial magnetic stimulation	124
Electrical fields for improvement of cerebral function in neurodegeneration	124
Neuroprotective effect of exercise	125
Hibernation and neuroprotection.....	125
Suspended animation and neuroprotection	126
3. Neuroprotection in Cerebrovascular Disease	127
Introduction.....	127
Pathophysiology of cerebral ischemia	127
Calcium overload	128
Ion channel dysfunction in stroke.....	128
Role of oxygen free radicals in cerebral ischemia	129
Role of nitric oxide in cerebral ischemia	129
Glutamate as a biomarker of stroke	129
Cerebral edema in stroke.....	129
Gene expression in response to cerebral ischemia	130
Induction of heat shock proteins in stroke	130
Role of cytokines and adhesion molecules in stroke	130
<i>Tumor necrosis factor-α</i>	<i>130</i>
<i>Interleukin-1 and IL-6</i>	<i>131</i>
<i>Adhesion molecules</i>	<i>131</i>
DNA damage and repair in cerebral ischemia.....	131
Role of neurotrophic factors in stroke	132
<i>Problems requiring investigation of the role of NTFs in stroke</i>	<i>132</i>
Role of Poly(ADP-ribose) polymerase (PARP) gene	132
Role of protease-activated receptor 1	133
Reperfusion injury after cerebral ischemia	133
Neuroprotection according to zones in cerebral infarction.....	133
Zone of ischemic infarction.....	133
Penumbra	134
Current management of stroke	134
Neuroprotection in stenosis of intracranial arteries	135
Neuroprotection in transient ischemic attacks	135
Neuroprotective therapies for stroke	135
α B-crystallin as a neuroprotectant in stroke.....	136
Acid-sensing ion channel blockers	137
AMPA receptor antagonists as neuroprotectives for stroke.....	137

<i>Zonampanel</i>	137
Antiapoptotic neuroprotectives	137
<i>NIM811</i>	137
<i>Creatine as neuroprotective in stroke</i>	138
<i>Lithium as a neuroprotective in stroke</i>	138
<i>TUDCA as a neuroprotective in stroke</i>	138
Coagulation inhibitors as neuroprotectives	138
<i>Heparin and enoxaparin</i>	139
<i>Warfarin vs dabigatran</i>	139
<i>Apixaban</i>	139
Antiepileptic drugs as neuroprotectives in stroke	140
<i>Tiagabine</i>	140
<i>Topiramate</i>	140
<i>Zonisamide</i>	140
Anti-HMGB1 monoclonal antibody	140
Antioxidant approaches	141
<i>Carnosine as a neuroprotective in stroke</i>	141
<i>Dehydroascorbic acid</i>	141
<i>Tocotrienols</i>	142
<i>Uric acid</i>	143
Antiglutamate compounds	143
<i>MRZ 2/576</i>	143
<i>L-Phenylalanine</i>	143
Arimoclolmol for stroke	143
Cardiac glycosides as neuroprotectives in stroke	144
Clenbuterol	144
Cox-2 inhibitors for ischemic stroke	144
Docosahexaenoic acid for ischemic stroke	144
Estrogen for stroke	145
Extendin-4	146
Flavones for neuroprotection in stroke	146
Granulocyte-macrophage colony-stimulating factor for cerebral ischemia	147
Modulation of histamine H ₂ -receptors	147
Inosine for stroke	147
Insulin-like growth factor-I	148
Intravenous immunoglobulin as neuroprotective in stroke	148
Ischemic preconditioning for neuroprotection in stroke	148
Ketone bodies for neuroprotection in stroke	149
Mineralocorticoid receptor blockade for neuroprotection	149
Multifunctional neuroprotective agents	149
Nasal delivery of neuroprotective agents in stroke	150
Neuroserpin as a neuroprotective in stroke	150
N-2-mercaptopropionyl glycine	150
NeuroAid	151
Neurotrophic factors as neuroprotectives for stroke	151
<i>AX200</i>	151
<i>Brain-derived neurotrophic factor</i>	151
<i>Fibroblast growth factor</i>	152
<i>Glial cell line-derived neurotrophic factor</i>	152
<i>Insulin-like growth factor-1</i>	152
<i>Neuregulin-1</i>	153
NO-based strategies for neuroprotection in cerebral ischemia	153
Perlecan domain V	154
Peroxisome proliferator-activated receptor- γ agonists	154
PGE ₂ EP2 receptor activation	154
Pioglitazone for reduction of stroke risk in diabetes	154
Progesterone	154
Proteasome inhibitors	155
Statins for prevention and neuroprotection in stroke	155
Sildenafil	156
Src receptor blockade	156
Stroke vaccine	156
SUN N4057	157
Thrombosis inhibitors	157
<i>Aspirin</i>	157
<i>Clopidogrel</i>	157
<i>Dipyridamole</i>	158
Vitamin E for neuroprotection in stroke	158
Neuroprotection in reperfusion injury	158
Prevention of hemorrhage following ischemic stroke	159
Non-pharmacological neuroprotective therapies for stroke	159

<i>Preconditioning for neuroprotection against cerebral ischemia</i>	159
<i>Hypothermia for neuroprotection in acute stroke</i>	160
<i>Hyperbaric oxygen therapy for neuroprotection in acute stroke</i>	160
<i>Infrared laser therapy for ischemic stroke</i>	161
<i>Neurostimulation of sphenopalatine ganglion</i>	162
<i>Neurosurgical procedures for neuroprotection in stroke</i>	162
<i>Neurorehabilitation in relation to neuroprotection in stroke</i>	163
Cell therapy for stroke	163
<i>Stem cell transplant for stroke</i>	163
<i>Immortalized cell grafts for stroke</i>	164
<i>Stimulation of intrinsic stem cells for repair of brain in stroke</i>	164
Neuroprotective vaccines for stroke.....	165
Gene therapy for neuroprotection in cerebrovascular disease	165
Regulation of microRNAs for neuroprotection in cerebral ischemia	167
RNAi-based therapy for neuroprotection in stroke	167
Neuroprotective therapies for cerebral ischemia: clinical trials	167
<i>Albumin</i>	168
<i>Free radical scavengers</i>	169
<i>DP-b99</i>	170
<i>Minocycline for neuroprotection in stroke</i>	170
<i>Perindopril</i>	171
Failed clinical trials of neuroprotection in stroke	171
<i>Ancrod</i>	172
<i>Aptiganel</i>	173
<i>Cerovive</i>	173
<i>Citicoline</i>	174
<i>Desmoteplase</i>	175
<i>Erythropoietin as a neuroprotective in stroke</i>	176
<i>SPD 502</i>	176
<i>Tirilazad mesylate</i>	176
<i>Selfotel</i>	176
<i>Lubeluzole</i>	177
<i>Nalmefene</i>	177
<i>Gavestinel</i>	177
<i>Nimodipine</i>	177
<i>Sipatrigine</i>	178
<i>Causes of failure of stroke trials</i>	178
<i>Measures for prevention of failures in stroke trials</i>	180
Design of acute stroke trial to facilitate drug approval	181
The ideal neuroprotective agent for stroke	181
Future prospects for neuroprotection in stroke	182
4. Neuroprotection in Traumatic Brain Injury	185
Introduction	185
Cerebral hypoxia/ischemia as a complication of trauma	185
Epidemiology of TBI	185
TBI in the military	186
Pathophysiology of TBI	186
Immediate damage following TBI.....	187
Cerebral edema following TBI.....	187
Delayed damage following TBI.....	187
Mechanism of axonal damage after TBI.....	187
Role of neuroinflammation in TBI.....	187
Molecular events following TBI.....	188
BBB damage after TBI	188
Chronic traumatic encephalopathy	188
Neurocognitive sequelae of TBI.....	189
Changes in neurotrophic factors following TBI.....	190
Changes in neurotransmitters following TBI.....	190
Proteomics of TBI.....	190
Genetic influences on outcome following TBI	191
Management of TBI	191
Control of intracranial pressure and cerebral edema	192
Corticosteroids	192
Neuroprotection in TBI	193
Antiepileptic drugs for prevention of seizures and neuroprotection	194
Antioxidants	194
Barbiturates	194
β - and γ -secretase inhibitors	195
Beta blockers	195
Bradykinin B ₂ antagonists	195

Cell cycle inhibitors for TBI.....	196
COX-2 inhibitors for neuroprotection in TBI	196
Cyclosporin for neuroprotection in TBI	196
Dexanabol for TBI	197
Erythropoietin for neuroprotection in TBI	197
Gold implants for neuroprotection in focal TBI	197
KN 38-7271	197
Levosimendan	198
Magnesium sulfate	198
Minocycline for TBI.....	198
Nutritional approaches to neuroprotection in TBI.....	198
<i>Branched chain amino acids to ameliorate cognitive impairment in TBI</i>	<i>199</i>
<i>Creatine for neuroprotection in TBI</i>	<i>199</i>
<i>Nicotinamide for neuroprotection in TBI</i>	<i>200</i>
<i>Omega 3 fatty acids as neuroprotectives in TBI</i>	<i>200</i>
Neurotrophic factors for TBI	200
Neurosteroids as neuroprotective agents for TBI	201
NMDA receptor antagonists	202
<i>NP-1.....</i>	<i>202</i>
Nogo-A inhibitor	203
Oxygen carriers for TBI.....	203
Polyethylene glycol for neuroprotection in TBI	204
Propofol for neuroprotection in TBI.....	204
Rapamycin as neuroprotective in TBI.....	204
Simvastatin as neuroprotective in TBI	204
Thyrotropin-releasing hormone analogs	205
Traxoprodil.....	205
Biological approaches to neuroprotection in TBI.....	205
Antisense approaches to TBI	205
Cell therapy for TBI.....	206
Gene therapy for TBI.....	206
Vaccines for TBI.....	206
Non-pharmaceutical approaches to neuroprotection in TBI	207
Hyperbaric oxygen therapy for TBI.....	207
Hypothermia	207
Reduction of microglial migration after TBI.....	207
Deep brain stimulation for TBI.....	207
Prophylactic neuroprotection against TBI	208
Role of helmets in protection against TBI	208
Role of physical exercise in protection against TBI.....	208
Clinical trials of neuroprotective agents in TBI	209
Ongoing clinical trials in TBI	209
Failed clinical trials in TBI.....	210
<i>Differences between clinical trials and studies in animal models of TBI.....</i>	<i>211</i>
<i>Subgroup analysis.....</i>	<i>211</i>
<i>Improving the clinical trial design.....</i>	<i>211</i>
<i>Clinical trials combining multiple treatment strategies.....</i>	<i>212</i>
<i>Shortening the trial time</i>	<i>212</i>
Conclusions and future prospects of neuroprotection in TBI.....	212
5. Neuroprotection in Spinal Cord Injury	215
Introduction.....	215
Pathophysiology of SCI	215
<i>Secondary mechanisms of SCI.....</i>	<i>216</i>
<i>Neurotrophic factor changes in SCI</i>	<i>217</i>
Management of SCI.....	218
Pharmacological neuroprotective agents for SCI	219
4-aminopyridine	219
Antibodies as neurite growth inhibitors in SCI.....	219
Bacterial enzyme chondroitinase ABC	219
Docosahexaenoic acid as neuroprotective in SCI	220
Erythropoietin as a neuroprotective in SCI	220
Free radical scavengers for neuroprotection in SCI	220
Gacyclidine.....	221
GYKI 52466.....	221
Immunosuppressants as neuroprotectants in SCI.....	221
Interleukin-10 for neuroprotection in SCI.....	221
Matrix metalloproteinase inhibitors for SCI	222
Methylprednisolone	222
Minocycline as neuroprotective in SCI.....	222
Neurotrophic factors for neuroprotection after SCI	223

<i>Promotion of regeneration of neurons in SCI</i>	223
Rho pathway and Rho antagonists in SCI	224
Selenium as a neuroprotective for SCI	224
Sialidase for enhancing recovery after SCI	224
Targeting the inflammatory response for neuroprotection in SCI	225
Uric acid as neuroprotective in SCI	225
Non-pharmacological approaches to SCI	225
Hyperbaric oxygen therapy	225
Hypothermia for SCI	225
Cell therapy for SCI	226
Autoimmune T cells against CNS myelin-associated peptide	226
Fetal neural grafts for SCI	226
Olfactory-ensheathing cells for SCI	226
Oligodendrocyte precursor cells for treatment of SCI	227
Schwann cell transplants for SCI.....	227
Transplantation of glial cells for SCI	227
Stem cells for SCI	227
<i>Bone marrow stem cells for SCI</i>	227
<i>Embryonic stem cells for SCI</i>	228
<i>Transplantation of induced pluripotent stem cells in SCI</i>	228
<i>Transplantation of MSCs for SCI</i>	229
<i>Transplantation of NSCs for SCI</i>	229
<i>Transdifferentiation of stem cells into cholinergic neurons for SCI</i>	230
Gene therapy for SCI	230
Combined approaches to spinal cord injury	231
Discovery of new targets for neuroprotective therapies in SCI	231
Clinical trials in SCI	232
6. Neuroprotection in Neurodegenerative Disorders	233
Introduction	233
Pathomechanism of neurodegeneration	233
Dual role of α -synuclein in neuroprotection and neurodegeneration	233
Lack of neurotrophic factors	234
Neuroinflammation in neurodegenerative disorders	234
Neurodegeneration associated with protein misfolding	234
<i>Modulation of neurodegeneration by molecular chaperones</i>	234
<i>Intrabodies targeting protein misfolding in neurodegeneration</i>	235
<i>Targeting proteins aggregation to prevent amyloid formation</i>	235
<i>Tau and neurodegeneration</i>	235
TDP-43 proteinopathy and neurodegenerative diseases	236
Role of apoptosis in neurodegenerative disorders	236
Role of glia in neurodegeneration	236
Role of metals in neurodegeneration	237
Viral infections and neurodegeneration	237
<i>AIDS and the nervous system</i>	237
<i>Avian influenza as cause of neurodegeneration</i>	238
Genetic disorders with neurodegeneration	239
Batten disease.....	239
Friedrich ataxia.....	240
<i>Pathomechanism of FA</i>	240
<i>Neuroprotection in FA</i>	240
Niemann-Pick type C disease.....	240
Creutzfeldt-Jakob disease	241
Approaches to neuroprotection in neurodegenerative disorders	242
Glutamate-based therapies for neurodegenerative disorders	242
Mitochondria permeability transition pore complex and neuroprotection	243
7. Neuroprotection in Parkinson Disease	245
Introduction	245
Epidemiology of Parkinson's disease	245
Pathophysiology of Parkinson's disease	245
Oxidative stress	246
Excitotoxicity	247
Asynchronous neuronal activity.....	247
Apoptosis	247
Role of neurotrophic factors	247
Role of misfolding proteins	247
Genetic factors in PD	248
Alteration of dopamine homeostasis	249
Neuroprotective strategies for PD based on pathomechanism	249
RNAi screening to identify neuroprotective genes in a PD model	250

Management of Parkinson's disease	251
Limitation of conventionally administered dopamine therapy	252
Treatment of dementia associated with PD	253
Neuroprotective therapy in PD.....	253
Neuroprotective effect of currently used drugs for PD	253
Pramipexole	253
Rasagiline mesylate.....	254
Ropinirole	255
Selegiline.....	255
Non-pharmacological strategies for neuroprotection in PD.....	256
Effect of exercise and environmental enrichment on PD	256
Low-calorie diet in PD	256
Development of neuroprotective therapies for PD	257
9-methyl- β -carboline.....	257
Adenosine A ₂ receptor antagonists	257
Antiapoptotic strategies for PD.....	258
Calcium channel blockers for PD	258
Cell therapies for PD.....	258
<i>Stem cells for PD</i>	<i>258</i>
<i>Activation of endogenous stem cells and neural precursors.....</i>	<i>259</i>
Cogane.....	260
Creatine and minocycline	260
Conserved dopamine neurotrophic factor for PD.....	260
Free radical scavengers for neuroprotection in Parkinson's disease.....	261
<i>Antioxidants</i>	<i>261</i>
<i>Melatonin</i>	<i>261</i>
<i>Tea extracts as neuroprotectives.....</i>	<i>261</i>
<i>Nicotine as a neuroprotective in PD</i>	<i>261</i>
Gene therapy for PD.....	262
<i>Implantation of genetically engineered cells</i>	<i>262</i>
<i>Gene therapy using GDNF and neurturin</i>	<i>263</i>
<i>Glutamic acid decarboxylase gene therapy</i>	<i>263</i>
<i>Parkin gene therapy</i>	<i>263</i>
<i>Concluding remarks about gene therapy for PD.....</i>	<i>264</i>
Heat shock protein 70	264
Neuroprotective effect of leucine-rich repeat kinase-2 inhibitors.....	265
Neuroprotective effect of DJ-1 protein	265
Neurotrophic factors.....	265
<i>Basic fibroblast growth factor for PD.....</i>	<i>265</i>
<i>BDNF for PD</i>	<i>266</i>
<i>GDNF for PD.....</i>	<i>266</i>
<i>MANF for PD.....</i>	<i>266</i>
<i>Neurturin for PD.....</i>	<i>267</i>
<i>Platelet derived growth factor.....</i>	<i>267</i>
<i>Clinical trials with NTFs.....</i>	<i>267</i>
Nrf2-mediated neuroprotection in PD.....	268
Omega-3 polyunsaturated fatty acids	268
RAB3B overexpression.....	268
RNAi therapy for PD	268
Safinamide.....	269
Sirtuin 2 inhibitors for neuroprotection in PD	269
Statins and PD.....	270
Targeting Bax.....	270
Vitamin D for neuroprotection in PD	270
Vaccine for PD	271
Clinical trials of neuroprotection in Parkinson's disease	271
Evaluation of neuroprotective therapies for PD.....	273
Current status and future challenges for neuroprotection in PD	274
8. Neuroprotection in Alzheimer Disease.....	277
Introduction.....	277
Pathomechanism of Alzheimer's disease	277
Role of glutamate transport dysfunction in AD	278
Role of neurotrophic factors in the pathomechanism of AD	278
Management of Alzheimer's disease	278
Neuroprotection in Alzheimer's disease	279
Inhibition of Aβ formation and aggregation	280
AN-1792	280
Cadmium telluride nanoparticles prevent A β fibril formation	281
Clioquinol.....	281
Colostrinin	282

FKBP52 for neuroprotection from Cu toxicity in AD	282
Monoclonal antibody m266.....	282
Phenserine	282
Secretase inhibitors	283
Inhibition of neuroinflammation	283
Etanercept	283
Neurotrophic factors/ gene therapy	284
NGF gene therapy	284
AL-108	285
Targeting plasminogen activator inhibitor type-1 gene.....	285
Estrogen and AD	286
Antioxidants	286
NSAIDS	286
Memantine.....	286
Dimebon	287
Cerebrolysin.....	288
Ginko biloba.....	288
Tetrahydrocannabinol for neuroprotection in AD	289
Ladostigil tartrate	290
Phosphodiesterase inhibitors as neuroprotectives.....	290
PPAR-γ agonists.....	290
Role of statins in reducing the risk of AD	290
Combined therapeutic approaches to AD	291
Clinical trials in AD.....	291
Future prospects of neuroprotection in AD	298
Mild cognitive impairment.....	299
Relation of MCI to AD	299
Neuroprotection in MCI	300

9. Neuroprotection in Huntington Disease 301

Introduction.....	301
Pathophysiology of HD.....	301
Management of Huntington's disease	302
Neuroprotection in Huntington's disease	303
Antipsychotic D ₂ and 5-HT _{1A} antagonists	304
Caspase inhibitors.....	304
Clioquinol for HD.....	304
Creatine for stabilizing bioenergetic defects.....	304
Cysteamine	305
Drugs that block inappropriate calcium release from neurons	305
Enhancing protease activity for clearance of mHtt	305
Eicosapentaenoic acid	305
Free radical scavengers	306
Histone deacetylase inhibitors	306
Inhibitors of polyglutamine aggregation HD	306
Pridopidine.....	307
Simvastatin as a neuroprotective in HD	307
Single chain Fv antibodies.....	308
SIRT1 activators for neuroprotection in HD.....	308
SIRT2 inhibitors for neuroprotection in HD	308
Synaptic activation of NMDA receptors.....	309
Tetrabenazine.....	309
Combinatorial therapy and targeting multiple pathways in HD	309
Cell transplants.....	310
Neurotrophic factors and gene therapy	310
RNAi therapy for Huntington's disease	311

10. Neuroprotection in Amyotrophic Lateral Sclerosis 313

Introduction.....	313
Pathophysiology of ALS	313
Neuroprotective therapies for ALS	315
Activated protein C.....	316
AEOL 10150	317
AIMSPRO	317
Anakinra	317
Arimocloamol for ALS	318
Antisense therapy	318
Creatine for ALS	318
Ceftriaxone for ALS	318
Coenzyme Q10 for ALS	319
COX-2 inhibitors for ALS	319

Dexpramipexole.....	319
Diallyl trisulfide.....	320
Erythropoietin for ALS	320
Gene therapy for ALS	320
Glatiramer acetate	321
Insulin-like growth factor	321
Ketogenic diet for neuroprotection in ALS.....	322
Lenalidomide	322
Lithium for neuroprotection in ALS	323
Methylcobalamin	323
Minocycline for ALS	323
Olesoxime as neuroprotective for ALS.....	323
ONO-2506 for ALS	324
Riluzole.....	324
RNAi-based therapy for ALS	324
Sodium phenylbutyrate.....	325
Stem cell therapy.....	325
Talampanel	325
Tamoxifen.....	325
Vaccination for ALS caused by SOD1 mutations	326
Vascular endothelial growth factor for ALS	326
Vitamin E for ALS.....	326
Clinical trials of neuroprotective therapies for ALS	327
Concluding remarks and future prospects.....	329

11. Neuroprotection in Miscellaneous Neurological Disorders 331

Introduction.....	331
Age-related dementia	331
Enhancing endogenous neurotrophic support of the aging brain	331
Pharmacological approaches for treatment of age-related dementia	332
Physical exercise to prevent decline of mental function with aging.....	333
Vascular dementia	333
Prediction of dementia in persons with vascular risk factors.....	333
Management of subcortical vascular dementia	334
Dementia with Lewy bodies	335
Neuroprotection in AIDS dementia	335
Multiple system atrophy.....	336
Epilepsy	336
Mechanisms of neuronal damage in epilepsy	336
Strategies for neuroprotection in epilepsy	337
Control of seizures by AEDs and neuroprotection	338
<i>Prevention of seizures by ketogenic diet.....</i>	<i>339</i>
Cell therapy for neuroprotection in epilepsy.....	340
<i>Cell therapy of posttraumatic epilepsy</i>	<i>340</i>
<i>Cell therapy for temporal lobe epilepsy</i>	<i>340</i>
<i>Cell therapy for pharmaco-resistant epilepsies</i>	<i>341</i>
Gene therapy for neuroprotection in epilepsy.....	341
Spinal and bulbar muscular atrophy	342
<i>Spinal muscular atrophy</i>	<i>342</i>
Multiple sclerosis	343
Introduction	343
Epidemiology of multiple sclerosis	343
Pathophysiology.....	344
Current management of multiple sclerosis.....	344
Specific therapies for MS based on pathomechanism	345
Neuroprotection in multiple sclerosis	345
Clinical trials of neuroprotective therapies for MS	346
Neuroprotection by control of progressive forms of multiple sclerosis.....	349
Neuroprotection by controlling autoimmune inflammation in the brain	349
Remyelination for neuroprotection in multiple sclerosis	350
Agents for neuroprotection in multiple sclerosis	350
<i>Angiotensin-II inhibitors.....</i>	<i>350</i>
<i>Antigliutamate agents</i>	<i>350</i>
<i>Antioxidants for neuroprotection in MS</i>	<i>350</i>
<i>Antisense and RNAi approaches to MS</i>	<i>351</i>
<i>Cell therapy for multiple sclerosis.....</i>	<i>351</i>
<i>Cladribine</i>	<i>353</i>
<i>Dalfampridine in MS</i>	<i>354</i>
<i>Dimethyl fumarate</i>	<i>354</i>
<i>DNA vaccine for MS.....</i>	<i>354</i>
<i>Erythropoietin as a neuroprotective in MS</i>	<i>355</i>

<i>Fingolimod (FTY720)</i>	355
<i>Fusokine composed of GM-CSF and IL-15 for immune suppression</i>	356
<i>Gene therapy for MS</i>	356
<i>Ibudilast for MS</i>	356
<i>IVIG for MS</i>	357
<i>Kinase inhibitors</i>	357
<i>Laquinimod</i>	357
<i>Monoclonal antibodies for MS</i>	357
<i>Natalizumab</i>	358
<i>Natural human antibodies for repair of myelin</i>	358
<i>Neurotrophic factors for multiple sclerosis</i>	359
<i>Oral immunomodulatory agents for MS</i>	360
<i>Recombinant T-cell ligands</i>	360
<i>Statins for MS</i>	360
<i>Teriflunomide</i>	361
<i>Concluding remarks on neuroprotection in MS</i>	361
Neuroprotection in transverse myelitis	361
Neuroprotection in decompression sickness	362
Neuroprotection in CSF circulatory disorders	363
Neuroprotection in hydrocephalus	363
Neuroprotection in normal pressure hydrocephalus	363
Neuroprotection in infections of the CNS	364
Neuroprotection in bacterial meningitis	364
<i>Mechanism of neural injury in bacterial meningitis</i>	364
<i>Strategies for neuroprotection</i>	365
Neuroprotection in cryptococcal meningitis.....	365
Neuroprotective approach to rabies	365
Neuroprotection in cerebral malaria.....	366
Neuroprotection in hypertensive encephalopathy	366
Neuroprotection in toxic encephalopathies	367
Hepatic encephalopathy	367
<i>Management of hepatic encephalopathy</i>	367
Encephalopathy due to organophosphorus poisoning	368
Neuroprotection against chemotherapy-induced brain damage	368
Neuroprotection against alcohol	369
<i>Alcoholic neurologic disorders</i>	369
<i>Fetal alcohol syndrome</i>	369
<i>Pathogenesis of alcohol-induced damage to the nervous system</i>	369
<i>Neuroprotection against neurotoxicity of alcohol</i>	370
Neuroprotection against radiation encephalopathy	370
Neuroprotection in hypoxia-ischemia	371
Neuroprotection in neonatal hypoxic-ischemic brain injury	371
<i>Minocycline for neonatal hypoxia-ischemia</i>	372
<i>Nicotinamide mononucleotide adenylyl transferase 1</i>	372
<i>Nitric oxide inhalation for neonatal hypoxia-ischemia</i>	372
<i>Plasminogen activator inhibitor-1 for neonatal hypoxia-ischemia</i>	373
<i>Recombinant erythropoietin for neonatal hypoxia-ischemia</i>	373
Neuroprotection in carbon monoxide poisoning	373
<i>Pathomechanism of CO poisoning as a basis for neuroprotection</i>	373
<i>Management of CO poisoning</i>	374
Syndrome of delayed post-hypoxic leukoencephalopathy	375
Neuroprotection of the fetus	375
Neuroprotection in sleep apnea	375
Neuroprotection in hypoglycemic coma	376
Neuroprotection in mitochondrial dysfunction	377
Mitochondrial permeability transition	377
Mitochondrial approaches for neuroprotection	378
Methylene blue	378
Role of nanolasers in evaluation of mitochondrial neuroprotectants	379
Neuroprotection in mitochondrial encephalopathies	379
Neuroprotection in psychiatric disorders	380
Cognitive impairment in schizophrenia.....	380
Neuroprotection in schizophrenia	380
Electroconvulsive therapy and neuroprotection	381
Neuroprotection in hearing loss	381
Causes of hearing loss	381
Pathomechanism of hearing loss	382
Prevention and treatment of hearing loss	382
<i>Hyperbaric oxygen for hearing loss</i>	383
<i>Stem cell therapy for hearing loss</i>	383
<i>Auditory hair cell replacement by gene therapy</i>	383

<i>Pharmaceutical approaches to hearing loss</i>	384
Neuroprotection of peripheral nerves	385
Neuroprotective agents for peripheral nerves	385
<i>Acetyl-L-carnitine for peripheral nerve injuries</i>	385
<i>Atorvastatin for peripheral nerve injuries</i>	385
<i>Erythropoietin for neuroprotection in peripheral nerve injuries</i>	386
Neuroprotection in peripheral nerve injuries	386
<i>Role of hyperbaric oxygen in peripheral nerve injuries</i>	386
<i>Role of neurotrophic factors in peripheral nerve injuries</i>	387
<i>Pharmacological approaches to Schwann cells</i>	387
<i>Role of gene therapy in neuroprotection of injured peripheral nerves</i>	387
<i>Schwann cell transplantation for peripheral nerve injury</i>	387
Peripheral neuropathy	388
<i>Neuroprotection in diabetic neuropathy</i>	388
<i>Cell therapy for neuroprotection in diabetic neuropathy</i>	388
<i>Gene therapy with zinc finger DNA-binding proteins</i>	389
<i>Neuroprotection in chemotherapy-induced neuropathy</i>	389
Chronic inflammatory demyelinating polyradiculoneuropathy	389
<i>Neuroprotection in CIDP</i>	390
12. Neuroprotection of the Optic nerve and the Retina	391
Introduction	391
Neuroprotection in optic neuropathy	391
Neuroprotection in optic neuritis	392
Neuroprotection in optic nerve trauma	392
Potential regeneration of the optic nerve	393
Subthreshold transpupillary thermotherapy for protection of RGCs	393
Neuroprotection of optic nerve in glaucoma	393
Aminoguanidine as a neuroprotective in glaucoma	395
Antiglutamate agents for neuroprotection of optic nerve	395
Betaxolol	395
NGF eye drops.....	395
Targeting A β in glaucoma treatment.....	396
TNF- α blockers for neuroprotection in glaucoma.....	396
Concluding remarks about neuroprotection in glaucoma.....	396
Neuroprotection in retinal ischemia	396
Endogenous neuroprotection in the retina	397
β -adrenoceptor antagonists.....	397
Brimonidine as a neuroprotective in ischemic retinopathy	398
Thioredoxin as a neuroprotective agent in retinal ischemia	398
Erythropoietin for neuroprotection of retinal ischemia	398
Gene therapy for retinal neuroprotection.....	399
Hyperbaric oxygen for central retinal artery occlusion.....	399
Protection against oxygen-induced retinopathy	399
Neuroprotection in macular degeneration	399
Epidemiology.....	399
Pathomechanism of AMD.....	400
Current treatment of AMD	400
Novel neuroprotective strategies against retinal degeneration.....	401
Antiangiogenic agents	402
Protection of retinal cells from oxidative-stress-induced apoptosis.....	402
Nutritional protection against AMD	403
Cell therapy for macular degeneration	403
<i>Retinal pigment epithelial cells</i>	403
<i>Encapsulated cells delivering CNTF for geographical retinal atrophy</i>	403
<i>Stem cells</i>	404
<i>Neural progenitor cells</i>	404
Gene therapy for retinal degeneration	404
RNAi-based treatments for AMD.....	405
Neuroprotection in proliferative diabetic retinopathy	406
Strategies for neuroprotection in diabetic retinopathy	406
RNAi-based approaches to diabetic retinopathy.....	406
Clinical trials for optic nerve and retinal neuroprotection	407
13. Neuroprotection during Anesthesia and Surgery	409
Introduction	409
Anesthetic agents as neuroprotectives	409
Barbiturates	409
<i>Thiopental</i>	410
Etomidate	411
Propofol	411

Ketamine	411
Gaseous anesthetics	412
<i>Isoflurane</i>	412
<i>Xenon</i>	412
Local anesthetics	413
Monitoring of CNS function during anesthesia and surgery	413
Monitoring of cerebral function	413
Monitoring of spinal cord function during spinal surgery	413
Neuroprotection during cardiovascular procedures	414
CNS complications of cardiac surgery	414
Neuroprotective strategies during cardiac surgery	415
<i>Neuroprotection during coronary artery bypass grafting</i>	417
<i>Neuroprotection before anticipated or induced cardiac arrest</i>	417
Surgery on the aorta	418
Spinal cord protection during cardiovascular surgery	418
Cerebral protection during organ transplantation surgery	418
Cerebral protection during neurosurgery	419
Cerebral angiography and endovascular surgery	419
Cerebral protection during surgery for arteriovenous malformations	419
Cerebral protection during surgery of intracranial aneurysms	419
Management of subarachnoid hemorrhage	420
<i>Vasospasm associated with subarachnoid hemorrhage</i>	420
Cerebral protection during carotid endarterectomy	422
Cerebral protection during surgery of brain tumors	422
Neuroprotective measures prior to surgery	423
Neuroprotection following surgery	423
14. Commercial Aspects of Neuroprotective Therapies	425
Introduction	425
The financial burden of CNS damage	425
Markets for neuroprotective therapies	425
Markets according to therapeutic areas	425
Values of neuroprotective therapies in major world markets	427
Unmet needs in neuroprotectives	428
Future prospects of neuroprotective therapies	429
Challenges in neuroprotective drug development	429
Promising areas of research in neuroprotection	429
<i>Autoreactive antibodies</i>	430
<i>Biological therapies for neuroprotection</i>	430
<i>Multidisciplinary approaches to neuroprotection</i>	430
15. References	431

Tables

Table 1-1: Historical landmarks in the development of neuroprotection	28
Table 1-2: Intrinsic neuroprotective factors	29
Table 1-3: Common features of pathophysiology of brain damage in diseases	36
Table 1-4: Place of neuroprotection in management of CNS disorders	37
Table 1-5: Indications for the use of neuroprotection	38
Table 2-1: A classification of neuroprotective agents	45
Table 2-2: The neuroprotective effect of antiepileptic drugs	53
Table 2-3: Neuroprotective affect of minocycline in animal models	57
Table 2-4: Classification of antioxidants or free radical scavengers with neuroprotective potential	64
Table 2-5: Role of erythropoietin in the nervous system	70
Table 2-6: Ionotropic glutamate receptors	75
Table 2-7: Classification of metabotropic glutamate receptors (mGluRs)	75
Table 2-8: Methods for neuroprotection based on nonpharmacological preconditioning	123
Table 3-1: Cerebrovascular diseases that are relevant to neuroprotection	127
Table 3-2: Neuroprotective strategies for stroke	135
Table 3-3: Neuroprotective gene transfer in models of cerebral ischemia	165
Table 3-4: Neuroprotective gene therapy in animal stroke models	166
Table 3-5: Neuroprotective agents in clinical development for acute cerebrovascular disease	168
Table 3-6: Some failed trials for neuroprotective therapy for stroke	171
Table 3-7: Preclinical assessment of neuroprotective agents in acute stroke models	180
Table 4-1: Current conventional management of traumatic brain injury	191
Table 4-2: Neuroprotective strategies for traumatic brain injury	193
Table 4-3: Ongoing or completed clinical trials for neuroprotection in TBI	209
Table 4-4: Discontinued or failed clinical trials for neuroprotection in TBI	210

Table 5-1: Secondary mechanisms in spinal cord injury	217
Table 5-2: Neuroprotective and regenerative approaches for SCI	218
Table 5-3: Clinical trials for neuroprotection in SCI	232
Table 6-1: Glutamate-based therapies in clinical development for neurodegenerative disorders	242
Table 7-1: Prevalence of Parkinson's disease in major markets 2011-2021	245
Table 7-2: Factors in the etiology of Parkinson's disease	245
Table 7-3: Strategies for the treatment of Parkinson's disease	251
Table 7-4: Current clinical trials of neuroprotective therapies for Parkinson disease	271
Table 7-5: Failed clinical trials of neuroprotective therapies for Parkinson disease	272
Table 7-6: Evaluation of neuroprotective agents for PD	273
Table 8-1: Cholinergic approaches to the treatment of Alzheimer's disease	279
Table 8-2: Neuroprotective agents for Alzheimer's disease	279
Table 8-3: Clinical trials for neuroprotection in Alzheimer disease	291
Table 8-4: Discontinued, failed or inconclusive clinical trials of Alzheimer disease	296
Table 8-5: Strategies for discovery of neuroprotective therapies for AD	298
Table 9-1: Neuroprotective approaches in HD	303
Table 10-1: Classification of neuroprotective agents for amyotrophic lateral sclerosis	316
Table 10-2: Clinical trials of neuroprotective therapies for ALS	327
Table 10-3: Failed or discontinued trials of neuroprotective therapies for ALS	328
Table 11-1: Therapeutic approaches to subcortical vascular dementia	334
Table 11-2: Pharmacological neuroprotection against the sequelae of seizures	338
Table 11-3: Neuroprotective effect of AEDs in animal models of status epilepticus (SE)	339
Table 11-4: Specific therapies for MS based on postulated pathomechanisms	345
Table 11-5: Approved neuroprotective therapies for multiple sclerosis	346
Table 11-6: Neuroprotective therapies for multiple sclerosis in clinical trials	347
Table 11-7: Failed or discontinued trials of neuroprotective therapies for ALS	347
Table 11-8: Approaches to neuroprotection in neonatal hypoxia-ischemia	371
Table 11-9: Drugs with neuroprotective effect at mitochondrial level	378
Table 11-10: Causes of sensorineural hearing impairment	381
Table 11-11: Strategies for prevention and treatment of sensorineural hearing loss	382
Table 11-12: Agents for neuroprotection of the peripheral nervous system	385
Table 12-1: Causes of optic neuropathy	391
Table 12-2: Neuroprotection of the optic nerve in glaucoma	394
Table 12-3: Strategies for neuroprotection in retinal ischemia	397
Table 12-4: Novel neuroprotective strategies against retinal degeneration	401
Table 12-5: Clinical trials for optic nerve and retinal neuroprotection	407
Table 13-1: CNS complications associated with cardiac procedures	414
Table 13-2: Strategies for protection of the brain during cardiac surgery	416
Table 13-3: Medical and surgical methods of cerebral vasospasm management	421
Table 13-4: Neuroprotection by prevention of vasospasm	421
Table 14-1: Neuroprotective market values 2011-2021	426
Table 14-2: Values of neuroprotective therapies in major world markets from 2011-21	427

Figures

Figure 2-1: Mechanism of neuroprotective effect of sigma-1 receptor agonists	52
Figure 2-2: NMDA receptor ion channel complex	79
Figure 2-3: Neuroprotective effect of galantamine	101
Figure 3-1: Some steps in the ischemic cascade and site of action of neuroprotectives	128
Figure 3-2: A roadmap for neuroprotection	181
Figure 4-1: Cascade of events following traumatic brain injury	186
Figure 5-1: Pathomechanism of acute spinal cord injury	216
Figure 7-1: Neuroprotective strategies against death of dopamine-containing neurons in PD	250
Figure 11-1: Common mechanisms of neural damage in cerebral ischemia and seizures	337
Figure 11-2: Role of neuroprotection in epilepsy and its treatment	338
Figure 8-1: Unmet therapeutic needs in neuroprotective therapies	428

Abbreviations

AAV	adeno-associated virus
ACh	acetylcholine
AD	Alzheimer's disease
ADCI	antibody-dependent cellular inhibition
ALS	amyotrophic lateral sclerosis
AMP	adenosine monophosphate
AMPA	amino-methyl proprionic acid
AED	antiepileptic drug
APC	activated protein C
ATA	atmospheric pressure absolute
atm	atmosphere
ATP	adenosine triphosphate
BBB	blood brain barrier
BDNF	brain derived neurotrophic factor
bFGF	basic fibroblast growth factor
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
ChE	choline esterase
CNS	central nervous system
CNTF	ciliary neurotrophic factor
CO	carbon monoxide
COX	cyclooxygenase
CREB	cAMP-response-element-binding protein
CSF	cerebrospinal fluid
DA	dopamine
DHA	Docosahexaenoic acid
EAATs	excitatory amino acid transporters
eNOS	endothelial nitric oxide synthase
EPO	erythropoietin
ESC	embryonic stem cell
FDA	Food and Drug Administration (USA)

FGF	fibroblast growth factor
GABA	gamma amino butyric acid
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GDNF	glial cell line-derived neurotrophic factor
GFAP	glial fibrillaary acidic protien
GPCR	G-protein-coupled receptor
HBO	hyperbaric oxygen
HD	Huntington's disease
HDAC	histone deacetylase
HSP	heat shock protein
HSV	herpes simplex virus
HT	hydroxytryptamine (serotonin)
ICAM-1	intercellular adhesion molecule-1
ICP	intracranial pressure
IFN	interferon
Ig	immunoglobulin
IGF	insulin-like growth factor
IL	interleukin
iNOS	inducible nitric oxide synthase
IOP	intraocular pressure
LIF	leukemia inhibitory factor
MAb	monoclonal antibody
MANF	mesencephalic-astrocyte-derived neurotrophic factor
MAO	monoamine oxidase
MAP	mitogen-activated protein
MAPK	mitogen-activated protein kinase
MCAO	middle cerebral artery occlusion
miRNA	microRNA
MMP	matrix metalloproteinase
mPT	mitochondrial permeability transition
MSCs	mesenchymal stem cells
MRI	magnetic resonance imaging