

# **Neuroprotection**

## **Part I: Drugs & Markets**

**By**

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

**November 2017**

**A Jain PharmaBiotech Report**

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

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

Prof. Jain's 473 publications include 28 books (5 as editor + 23 as author) and 50 special reports, which have covered important areas in biotechnology, gene therapy and biopharmaceuticals. As associate editor and contributing author of MedLink Neurology (San Diego, California), he is responsible for writing and yearly updating of 160 articles for continuing education of neurologists in an electronic encyclopedia of neurology. He has also written the Textbook of Gene Therapy, which was translated into Chinese, and a book on gene therapy companies published in 2000 by John Wiley & Sons. Prof. Jain has edited "Drug Delivery Systems" (Humana/Springer, 2008; 2<sup>nd</sup> ed 2014) and "Drug Delivery to the Central Nervous System", (Springer/Humana 2010). His recent books include "Handbook of Nanomedicine" (Springer/Humana 2008, Chinese edition by Peking University Press, 2011; 3<sup>rd</sup> ed Springer 2017), "Drug-induced Neurological Disorders, 3<sup>rd</sup> ed" (Hogrefe 2011), "Textbook of Personalized Medicine" (Springer 2009; Japanese ed 2012; 2<sup>nd</sup> ed Springer, 2015), "Handbook of Biomarkers" (Springer 2010; Chinese edition, Chemical Industry Press 2016, 2<sup>nd</sup> ed Springer 2017), "Handbook of Neuroprotection" (Springer 2011), and "Applications of Biotechnology in Neurology" (Springer 2013). He has also edited "Applied Neurogenomics" (Springer 2015).

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

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

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

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

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

# TABLE OF CONTENTS

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

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

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

<i>Piracetam</i> .....	117
<b>Nutraceuticals and naturally-derived compounds</b> .....	<b>117</b>
Cinnamon .....	117
Coffee .....	118
Creatine.....	118
Curcumin/curry .....	119
<i>Mechanism of neuroprotective effect of curcumin</i> .....	119
Flavonoids .....	119
Glyceryltriacetate.....	120
Green tea .....	120
Herbal preparations.....	120
<i>Flavonoid wogonin</i> .....	120
<i>Ginseng</i> .....	121
Nicotinamide .....	121
Punicalagin from pomegranate .....	121
Resveratrol .....	121
<b>Osmotic diuretics</b> .....	<b>122</b>
Mannitol .....	122
Osteopontin .....	123
<b>Oxygen therapeutics</b> .....	<b>123</b>
Oxygen carriers .....	123
Hemoglobin-based oxygen carriers.....	124
Perfluorocarbons as oxygen carriers .....	124
Hyperbaric oxygen therapy .....	125
<b>P7C3 compounds</b> .....	<b>125</b>
<b>Peptides</b> .....	<b>126</b>
C3-derived peptide for neuroprotection and neuroregeneration .....	126
Corticotropin-releasing hormone.....	126
Thyrotropin-releasing hormone.....	126
Vasoactive intestinal peptide .....	127
<b>Pharmacological preconditioning</b> .....	<b>127</b>
<b>PPARs as drug targets for neuroprotection</b> .....	<b>128</b>
<b>Proteins</b> .....	<b>128</b>
Amyloid precursor protein .....	128
Protein kinase C activators.....	129
<b>Riluzole</b> .....	<b>129</b>
<b>Role of RNA interference in neuroprotection</b> .....	<b>129</b>
Role of miRNA in neuroprotection.....	130
<b>Sigma receptor agonists as neuroprotective agents</b> .....	<b>130</b>
<b>SIRT group of proteins</b> .....	<b>131</b>
<b>Statins</b> .....	<b>131</b>
<b>Steroids</b> .....	<b>132</b>
Dehydroepiandrosterone.....	132
HF0220 .....	133
<b>Sulforaphane</b> .....	<b>133</b>
<b>Tauroursodeoxycholic acid</b> .....	<b>133</b>
<b>Tetanus toxin as a neuroprotective agent</b> .....	<b>134</b>
<b>Thrombolytic agents as neuroprotective agents</b> .....	<b>134</b>
<b>Uncoupling protein 2</b> .....	<b>134</b>
<b>Vaccines as neuroprotectives</b> .....	<b>135</b>
<b>Vitamins as neuroprotective agents</b> .....	<b>135</b>
Vitamin B12 .....	135
Vitamin D .....	136
<b>Non-pharmacological approaches to neuroprotection</b> .....	<b>136</b>
Caloric restriction.....	136
Cerebral exercise .....	136
<i>Bilingualism for prevention of decline of mental function</i> .....	136
Electrical fields for improvement of cerebral function in neurodegeneration .....	137
Environmental enrichment .....	137
Hypothermia .....	138
<i>Limitations of hypothermia</i> .....	138
<i>Hypothermic neuroprotection in hypoxia-ischemia</i> .....	139
Ketogenic diet .....	139
Mediterranean diet.....	140
Nonpharmacological preconditioning for neuroprotection.....	140
Physical exercise.....	140
Suspended animation and neuroprotection .....	141
Transcranial magnetic stimulation .....	142
<b>3. Neuroprotection in Cerebrovascular Disease</b> .....	<b>143</b>
<b>Introduction</b> .....	<b>143</b>

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

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



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

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

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

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

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

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

## **7. Neuroprotection in Parkinson Disease ..... 287**

<b>Introduction</b> .....	<b>287</b>
<b>Epidemiology of Parkinson's disease</b> .....	<b>287</b>
<b>Pathophysiology of Parkinson's disease</b> .....	<b>287</b>
Alteration of dopamine homeostasis .....	288
Apoptosis.....	288
Asynchronous neuronal activity .....	288
Disruption of iron homeostasis.....	289
Excitotoxicity.....	289
Genetic factors in PD .....	289
Oxidative stress.....	290
Role of neurotrophic factors .....	291
Role of misfolding proteins.....	291
Synaptic vesicle glycoprotein 2C disruption in PD .....	292
<b>Neuroprotective strategies for PD based on pathomechanism</b> .....	<b>292</b>
A genetic animal model of PD for testing neuroprotective strategies .....	293
Aldehyde dehydrogenase 1 protects nigrostriatal dopaminergic neurons .....	294
RNAi screening to identify neuroprotective genes in a PD model .....	294
Strategies to stop aggregation of $\alpha$ -synuclein .....	294
<b>Management of Parkinson's disease</b> .....	<b>295</b>
Limitation of conventionally administered dopamine therapy .....	296
<b>Neuroprotective therapy in PD</b> .....	<b>297</b>
<b>Neuroprotective effect of currently used drugs for PD</b> .....	<b>297</b>
Pramipexole .....	297
Rasagiline mesylate .....	298
Ropinirole .....	299
Rivastigmine for treatment of dementia and falls associated with PD .....	299
Selegiline.....	299
<b>Non-pharmacological strategies for neuroprotection in PD</b> .....	<b>300</b>
Deep brain stimulation for PD.....	300
Effect of exercise and environmental enrichment on PD .....	301
Low-calorie diet in PD.....	301
<b>Development of neuroprotective therapies for PD</b> .....	<b>301</b>
2B3-201 for targeted delivery of methylprednisolone.....	302
9-methyl- $\beta$ -carboline.....	302
Adenosine $A_{A2}$ receptor antagonists .....	302
Antiapoptotic strategies for PD .....	303
ATP13A2 activation .....	303
Augmenting CNS glucocerebrosidase activity .....	303
$\beta$ 2-Adrenoreceptor agonists .....	304
Calcium channel blockers for PD .....	304
Cell therapies for PD.....	304
<i>Stem cells for PD</i> .....	304
<i>Activation of endogenous stem cells and neural precursors</i> .....	305
Cogane.....	306
Creatine and minocycline .....	306
Conserved dopamine neurotrophic factor for PD.....	306
Doxycycline as a neuroprotectant in PD.....	307
Free radical scavengers for neuroprotection in Parkinson's disease.....	307
<i>Antioxidants</i> .....	307
<i>Diapocynin</i> .....	307
<i>Tea extracts as neuroprotectives</i> .....	308
Gene therapy for PD.....	308
<i>Implantation of genetically engineered cells</i> .....	309
<i>Gene therapy using GDNF and neurturin</i> .....	309
<i>Glutamic acid decarboxylase gene therapy</i> .....	310

<i>Parkin gene therapy</i> .....	310
<i>Concluding remarks about gene therapy for PD</i> .....	311
Heat shock protein 70 .....	311
Liver X receptor $\beta$ agonists.....	311
Melatonin as a neuroprotectant in PD .....	312
Nicotine as a neuroprotective in PD .....	312
Nilotinib for PD .....	312
Neuroprotective effect of leucine-rich repeat kinase-2 inhibitors .....	313
Neuroprotective effect of DJ-1 protein .....	313
Neurotrophic factors.....	313
<i>Basic fibroblast growth factor for PD</i> .....	314
<i>BDNF for PD</i> .....	314
<i>GDNF for PD</i> .....	314
<i>MANF for PD</i> .....	315
<i>Neurturin for PD</i> .....	315
<i>Platelet derived growth factor</i> .....	315
<i>Clinical trials with NTFs</i> .....	316
Nrf2-mediated neuroprotection in PD.....	316
Nuclear receptor-related 1:Retinoid X receptor $\alpha$ activation .....	316
Omega-3 polyunsaturated fatty acids .....	316
RAB3B overexpression.....	317
RNAi therapy for PD .....	317
Safinamide.....	317
Sirtuin 2 inhibitors for neuroprotection in PD .....	318
Squalamine and PD .....	318
Statins and PD.....	319
Targeting Bax.....	319
Vitamin D for neuroprotection in PD .....	319
Vaccine for PD .....	320
<b>Clinical trials of neuroprotection in Parkinson's disease .....</b>	<b>320</b>
<b>Evaluation of neuroprotective therapies for PD .....</b>	<b>322</b>
<b>Current status and future challenges for neuroprotection in PD .....</b>	<b>323</b>

<b>8. Neuroprotection in Alzheimer Disease .....</b>	<b>325</b>
<b>Introduction .....</b>	<b>325</b>
<b>Pathomechanism of Alzheimer's disease .....</b>	<b>325</b>
Role of glutamate transport dysfunction in AD .....	326
Role of neurotrophic factors in the pathomechanism of AD .....	326
<b>Management of Alzheimer's disease .....</b>	<b>326</b>
<b>Neuroprotection in Alzheimer's disease .....</b>	<b>327</b>
<b>Inhibition of A<math>\beta</math> formation and aggregation.....</b>	<b>328</b>
AN-1792 .....	328
Clioquinol.....	329
Colostrinin .....	329
FKBP52 for neuroprotection from Cu toxicity in AD.....	330
Monoclonal antibody m266.....	330
Phenserine.....	330
Secretase inhibitors.....	331
<b>Inhibition of neuroinflammation .....</b>	<b>331</b>
Etanercept .....	331
<b>Neurotrophic factors for neuroprotection in AD .....</b>	<b>332</b>
AL-108 .....	332
NGF gene therapy .....	332
Small molecule compounds binding to neurotrophin receptor p75NTR.....	333
Targeting plasminogen activator inhibitor type-1 gene.....	334
<b>Estrogen and AD .....</b>	<b>334</b>
<b>Antioxidants .....</b>	<b>335</b>
NSAIDS .....	335
<b>Melatonin for AD .....</b>	<b>335</b>
<b>Memantine.....</b>	<b>335</b>
<b>Dimebon .....</b>	<b>336</b>
<b>Cerebrolysin .....</b>	<b>337</b>
<b>Curcumin as a neuroprotectant in Alzheimer disease .....</b>	<b>337</b>
<b>Ginko biloba.....</b>	<b>337</b>
<b>Tetrahydrocannabinol for neuroprotection in AD .....</b>	<b>338</b>
<b>Ladostigil tartrate.....</b>	<b>339</b>
<b>Phosphodiesterase inhibitors as neuroprotectives.....</b>	<b>339</b>
<b>PPAR-<math>\gamma</math> agonists .....</b>	<b>339</b>
<b>Role of statins in reducing the risk of AD .....</b>	<b>340</b>
<b>Combined therapeutic approaches to AD .....</b>	<b>340</b>
<b>Clinical trials in AD.....</b>	<b>340</b>

<b>Future prospects of neuroprotection in AD .....</b>	<b>349</b>
<b>Mild cognitive impairment .....</b>	<b>349</b>
Relation of MCI to AD .....	350
Neuroprotection in MCI .....	350
<b>9. Neuroprotection in Huntington Disease .....</b>	<b>353</b>
<b>Introduction .....</b>	<b>353</b>
<b>Pathophysiology of HD.....</b>	<b>353</b>
<b>Management of Huntington's disease .....</b>	<b>355</b>
<b>Neuroprotection in Huntington's disease .....</b>	<b>355</b>
Antipsychotic D <sub>2</sub> and 5-HT <sub>1A</sub> antagonists .....	356
Caspase inhibitors.....	356
Clioquinol for HD.....	357
Creatine for stabilizing bioenergetic defects.....	357
Cysteamine.....	357
Drugs that block inappropriate calcium release from neurons .....	357
Enhancing protease activity for clearance of mHtt.....	358
Eicosapentaenoic acid.....	358
Free radical scavengers .....	358
Histone deacetylase inhibitors .....	359
Inhibitors of polyglutamine aggregation HD .....	359
Metal-protein attenuating compounds.....	360
Pridopidine.....	360
RRAS signaling pathway inhibition.....	360
Simvastatin as a neuroprotective in HD .....	361
Single chain Fv antibodies .....	361
SIRT1 activators for neuroprotection in HD .....	361
SIRT2 inhibitors for neuroprotection in HD .....	362
Synaptic activation of NMDA receptors.....	362
Targeting mutant huntingtin protein.....	362
Tetrabenazine .....	363
Combinatorial therapy and targeting multiple pathways in HD .....	363
Cell therapy for HD .....	363
<i>Cell transplants for HD.....</i>	<i>363</i>
<i>Stem cell-based therapy for HD .....</i>	<i>364</i>
Neurotrophic factors and gene therapy .....	365
RNAi and antisense therapies for Huntington's disease .....	365
<b>10. Neuroprotection in Amyotrophic Lateral Sclerosis .....</b>	<b>367</b>
<b>Introduction .....</b>	<b>367</b>
<b>Pathophysiology of ALS .....</b>	<b>367</b>
<b>Neuroprotective therapies for ALS.....</b>	<b>372</b>
Activated protein C .....	373
AEOL 10150 .....	373
AIMSPRO .....	373
Anakinra.....	374
Antisense therapy .....	374
Arimoclomol for ALS.....	374
Ceftriaxone for ALS .....	375
Coenzyme Q10 for ALS.....	375
COX-2 inhibitors for ALS .....	375
Creatine for ALS .....	376
Dexpramipexole.....	376
Diallyl trisulfide.....	376
Edaravone for ALS .....	377
Erythropoietin for ALS .....	377
Gene therapy for ALS .....	377
Glatiramer acetate .....	378
GM602 .....	378
Insulin-like growth factor .....	378
Ketogenic diet for neuroprotection in ALS.....	379
Lenalidomide.....	379
Lithium for neuroprotection in ALS .....	380
Masitinib .....	380
Melatonin for ALS.....	380
Methylcobalamin.....	381
Minocycline for ALS .....	381
Olesoxime as neuroprotective for ALS.....	381
ONO-2506 for ALS .....	381
Riluzole .....	382
RNAi-based therapy for ALS .....	382

Sodium phenylbutyrate.....	382
Stem cell therapy.....	383
<i>Clinical applications</i> .....	383
<i>Stem cell-based drug discovery for ALS</i> .....	383
<i>Suppressors of mTDP-43 toxicity</i> .....	384
Talampanel.....	384
Tamoxifen.....	385
Vaccination for ALS caused by SOD1 mutations.....	385
Vascular endothelial growth factor for ALS.....	385
Vitamin E for ALS.....	386
<b>Clinical trials of neuroprotective therapies for ALS.....</b>	<b>386</b>
<b>Concluding remarks and future prospects.....</b>	<b>389</b>

## **11. Neuroprotection in Miscellaneous Neurological Disorders ..... 391**

<b>Introduction.....</b>	<b>391</b>
<b>Neuroprotection in synaptopathies.....</b>	<b>391</b>
Neuroprotection in fragile X syndrome.....	392
<b>Neuroprotection in dementia.....</b>	<b>392</b>
Age-related dementia.....	392
<i>Aging brain and oxidative stress</i> .....	393
<i>Enhancing endogenous neurotrophic support of the aging brain</i> .....	393
<i>Hsp70 and age-related neurodegeneration</i> .....	393
<i>Pharmacological approaches for treatment of age-related dementia</i> .....	394
<i>Physical exercise to prevent decline of mental function with aging</i> .....	395
Vascular dementia.....	395
<i>Prediction of dementia in persons with vascular risk factors</i> .....	395
<i>Management of subcortical vascular dementia</i> .....	396
Dementia with Lewy bodies.....	397
Neuroprotection in AIDS dementia.....	397
<b>Multiple system atrophy.....</b>	<b>398</b>
<b>Epilepsy.....</b>	<b>398</b>
Mechanisms of neuronal damage in epilepsy.....	398
Strategies for neuroprotection in epilepsy.....	399
AEDs and neuroprotection.....	400
Cell therapy for neuroprotection in epilepsy.....	401
<i>Cell therapy of posttraumatic epilepsy</i> .....	402
<i>Cell therapy for temporal lobe epilepsy</i> .....	402
<i>Cell therapy for pharmaco-resistant epilepsies</i> .....	402
Gene therapy for neuroprotection in epilepsy.....	403
Hyaluronan-based preservation of brain ECS volume.....	404
Hypothermia for neuroprotection in status epilepticus.....	404
Ketogenic diet for prevention of seizures.....	404
miR-211 as an attenuator of cholinergic-mediated seizures.....	404
<b>Multiple sclerosis.....</b>	<b>405</b>
Introduction.....	405
Epidemiology of multiple sclerosis.....	405
Pathophysiology.....	405
Current management of multiple sclerosis.....	406
Specific therapies for MS based on pathomechanism.....	407
Neuroprotection in multiple sclerosis.....	407
Clinical trials of neuroprotective therapies for MS.....	409
Neuroprotection by control of progressive forms of multiple sclerosis.....	410
Neuroprotection by controlling autoimmune inflammation in the brain.....	410
Neuroprotection by sealing the BBB with imatinib.....	410
TRPM4 cation channel blockers.....	411
Remyelination for neuroprotection in multiple sclerosis.....	411
Agents for neuroprotection in multiple sclerosis.....	411
<i>Angiotensin-II inhibitors</i> .....	411
<i>Antiglutamate agents</i> .....	412
<i>Antioxidants for neuroprotection in MS</i> .....	412
<i>Antisense and RNAi approaches to MS</i> .....	412
<i>B cell depletion therapy</i> .....	412
<i>Cell therapy for multiple sclerosis</i> .....	413
<i>Cannabinoids for neuroprotection in MS</i> .....	416
<i>Cladribine</i> .....	416
<i>Curcumin as a neuroprotectant in multiple sclerosis</i> .....	416
<i>Cytokine-directed therapies in MS</i> .....	417
<i>Dalfampridine in MS</i> .....	417
<i>Dimethyl fumarate</i> .....	417
<i>DNA vaccine for MS</i> .....	418
<i>Erythropoietin as a neuroprotective in MS</i> .....	418

<i>Fingolimod</i> .....	418
<i>Fusokine composed of GM-CSF and IL-15 for immune suppression</i> .....	419
<i>Gene therapy for MS</i> .....	419
<i>Ibudilast for MS</i> .....	420
<i>Iron chelators</i> .....	420
<i>IVIg for MS</i> .....	420
<i>Kinase inhibitors</i> .....	421
<i>Laquinimod</i> .....	421
<i>Melatonin for MS</i> .....	421
<i>Minocycline for MS</i> .....	421
<i>Monoclonal antibodies for MS</i> .....	422
<i>Natalizumab</i> .....	423
<i>Natural human antibodies for repair of myelin</i> .....	423
<i>Neurotrophic factors for multiple sclerosis</i> .....	424
<i>Nimodipine</i> .....	425
<i>Oral immunomodulatory agents for MS</i> .....	425
<i>Protein kinase C<math>\beta</math> as a therapeutic target for stabilizing BBB in MS</i> .....	425
<i>Recombinant T-cell ligands</i> .....	425
<i>Statins for MS</i> .....	426
<i>Teriflunomide</i> .....	426
<i>Tolerance-directed immunotherapy for MS</i> .....	426
Concluding remarks and future prospects for neuroprotection in MS .....	427
<b>Neuroprotection in anti-NMDA receptor encephalitis</b> .....	<b>428</b>
<b>Neuroprotection in transverse myelitis</b> .....	<b>428</b>
<b>Neuroprotection in decompression sickness</b> .....	<b>428</b>
<b>Neuroprotection in victims of drowning</b> .....	<b>429</b>
<b>Neuroprotection in CSF circulatory disorders</b> .....	<b>430</b>
Neuroprotection in hydrocephalus .....	430
Neuroprotection in normal pressure hydrocephalus .....	430
<b>Neuroprotection in infections of the CNS</b> .....	<b>431</b>
Neuroprotection in bacterial meningitis .....	431
<i>Mechanism of neural injury in bacterial meningitis</i> .....	431
<i>Strategies for neuroprotection</i> .....	432
Neuroprotection in cryptococcal meningitis .....	432
Neuroprotective approach to rabies .....	433
Neuroprotection in cerebral malaria .....	433
<b>Neuroprotection in complications of systemic disorders</b> .....	<b>433</b>
Neurological complications of cardiovascular disorders .....	433
<i>Neuroprotection after myocardial infarction</i> .....	433
<i>Neuroprotection in hypertensive encephalopathy</i> .....	434
<i>Management of hypertension to prevent dementia</i> .....	434
Neuroprotection in complications of diabetes .....	435
<i>Neuroprotection in hypoglycemic coma</i> .....	435
<i>Neuroprotection in diabetic retinopathy</i> .....	436
Neurological complications of liver disorders .....	436
<i>Hepatic encephalopathy</i> .....	436
<i>Bilirubin encephalopathy</i> .....	437
<b>Neuroprotection in neurological complications of renal disease</b> .....	<b>438</b>
<b>Neuroprotection in toxic encephalopathies</b> .....	<b>439</b>
Encephalopathy due to organophosphorus poisoning .....	439
Neuroprotection against chemotherapy-induced brain damage .....	439
Neuroprotection against alcohol .....	440
<i>Alcoholic neurologic disorders</i> .....	440
<i>Fetal alcohol syndrome</i> .....	440
<i>Pathogenesis of alcohol-induced damage to the nervous system</i> .....	441
<i>Neuroprotection against neurotoxicity of alcohol</i> .....	441
<b>Neuroprotection against exposure to therapeutic radiation</b> .....	<b>441</b>
Neuroprotection against radiation encephalopathy .....	441
Role of SOD in protection against radiation-induced hippocampal dysfunction .....	442
Catalase reduces mitochondrial ROS for neuroprotection from proton irradiation .....	442
<b>Neuroprotection in hypoxia-ischemia</b> .....	<b>443</b>
<b>Neuroprotection of the fetus and the neonate</b> .....	<b>443</b>
Neuroprotection in preterm babies .....	443
Neuroprotection in neonatal hypoxic-ischemic brain injury .....	444
<i>Pathomechanism of neonatal hypoxic-ischemic brain injury</i> .....	444
<i>Management of neonatal hypoxia-ischemia</i> .....	444
<i>Approaches to neuroprotection in neonatal hypoxia-ischemia</i> .....	444
<i>Hyperbaric oxygen for neonatal hypoxia-ischemia</i> .....	445
<i>Hypothermia for neonatal hypoxia-ischemia</i> .....	445
<i>Melatonin for neonatal hypoxia-ischemia</i> .....	446
<i>Minocycline for neonatal hypoxia-ischemia</i> .....	446



<i>Nicotinamide mononucleotide adenylyl transferase 1</i> .....	446
<i>Nitric oxide inhalation for neonatal hypoxia-ischemia</i> .....	446
<i>Plasminogen activator inhibitor-1 for neonatal hypoxia-ischemia</i> .....	446
<i>Recombinant erythropoietin for neonatal hypoxia-ischemia</i> .....	447
<b>Neuroprotection in carbon monoxide poisoning</b> .....	<b>447</b>
Pathomechanism of CO poisoning as a basis for neuroprotection.....	447
Management of CO poisoning .....	448
<b>Neuroprotection after cardiac arrest</b> .....	<b>449</b>
<b>Neuroprotection in delayed post-hypoxic leukoencephalopathy</b> .....	<b>449</b>
<b>Neuroprotection in sleep apnea</b> .....	<b>450</b>
<b>Neuroprotection in mitochondrial dysfunction</b> .....	<b>450</b>
Mitochondrial permeability transition .....	451
Mitochondrial approaches for neuroprotection.....	451
Methylene blue .....	452
Role of nanolasers in evaluation of mitochondrial neuroprotectants .....	452
Neuroprotection in mitochondrial encephalopathies .....	453
<b>Neuroprotection in psychiatric disorders</b> .....	<b>453</b>
Cognitive impairment in schizophrenia.....	453
Electroconvulsive therapy and neuroprotection .....	454
Neuroprotection in schizophrenia .....	454
Neuroplasticity and neuroprotection in stress-induced psychiatric disorders.....	454
<b>Neuroprotection in hearing loss</b> .....	<b>455</b>
Causes of hearing loss.....	455
Pathomechanism of hearing loss .....	456
Prevention and treatment of hearing loss.....	456
<i>Hyperbaric oxygen for hearing loss</i> .....	457
<i>Stem cell therapy for hearing loss</i> .....	457
<i>Auditory hair cell replacement by gene therapy</i> .....	457
<i>Pharmaceutical approaches to hearing loss</i> .....	458
<b>Neuroprotection of peripheral nerves</b> .....	<b>459</b>
Neuroprotective agents for peripheral nerves .....	459
<i>Acetyl-L-carnitine for peripheral nerve injuries</i> .....	460
<i>Atorvastatin for peripheral nerve injuries</i> .....	460
<i>Erythropoietin for neuroprotection in peripheral nerve injuries</i> .....	460
Neuroprotection in peripheral nerve injuries .....	461
<i>Role of hyperbaric oxygen in peripheral nerve injuries</i> .....	461
<i>Role of neurotrophic factors in peripheral nerve injuries</i> .....	461
<i>Pharmacological approaches to Schwann cells</i> .....	461
<i>Role of gene therapy in neuroprotection of injured peripheral nerves</i> .....	461
<i>Schwann cell transplantation for peripheral nerve injury</i> .....	462
<i>Targeting Wallerian degeneration slow protein for neuroprotection</i> .....	462
Peripheral neuropathy .....	462
<i>Neuroprotection in diabetic neuropathy</i> .....	462
<i>Cell therapy for neuroprotection in diabetic neuropathy</i> .....	463
<i>Gene therapy with zinc finger DNA-binding proteins</i> .....	463
<i>Neuroprotection in chemotherapy-induced neuropathy</i> .....	463
Chronic inflammatory demyelinating polyradiculoneuropathy.....	464
<i>Neuroprotection in CIDP</i> .....	464
<b>12. Neuroprotection of the Optic nerve and the Retina</b> .....	<b>465</b>
<b>Introduction</b> .....	<b>465</b>
<b>Optic neuropathy</b> .....	<b>465</b>
Pathophysiology .....	465
Neuroprotection in optic neuritis .....	466
<i>Evaluating efficacy of drugs for optic neuritis</i> .....	467
<i>Flupirtine</i> .....	467
<i>Sodium channel blockers</i> .....	468
<i>Resveratrol</i> .....	468
<b>Neuroprotection in optic nerve trauma</b> .....	<b>468</b>
Potential regeneration of the optic nerve.....	469
Subthreshold transpupillary thermotherapy for protection of RGCs.....	469
<b>Neuroprotection of optic nerve in glaucoma</b> .....	<b>469</b>
Aminoguanidine as a neuroprotective in glaucoma .....	471
Antiglutamate agents for neuroprotection of optic nerve .....	471
Betaxolol .....	471
NGF eye drops.....	471
Targeting A $\beta$ in glaucoma treatment.....	472
TNF- $\alpha$ blockers for neuroprotection in glaucoma .....	472
Concluding remarks about neuroprotection in glaucoma.....	472
<b>Neuroprotection in retinal ischemia</b> .....	<b>472</b>
$\beta$ -adrenoceptor antagonists.....	473

Brimonidine as a neuroprotective is ischemic retinopathy .....	473
Endogenous neuroprotection in the retina .....	474
Erythropoietin for neuroprotection of retinal ischemia .....	474
Gene therapy for retinal neuroprotection .....	474
Hyperbaric oxygen for central retinal artery occlusion .....	475
Levodopa for treating non-arteritic anterior ischemic optic neuropathy .....	475
Thioredoxin as a neuroprotective agent in retinal ischemia .....	475
<b>Protection against oxygen-induced retinopathy .....</b>	<b>475</b>
<b>Neuroprotection in macular degeneration .....</b>	<b>476</b>
Epidemiology .....	476
Pathomechanism of AMD .....	476
Current treatment of AMD .....	476
Novel neuroprotective strategies against retinal degeneration .....	478
Antiangiogenic agents .....	479
Humanized MAb against A $\beta$ .....	479
LXR agonists .....	480
Neurotrophic factors for neuroprotection in AMD .....	480
<i>CNTF for neuroprotection in AMD .....</i>	<i>480</i>
<i>N-acetylserotonin derivatives .....</i>	<i>480</i>
Nutritional protection against AMD .....	480
Progestogenic hormones .....	481
Protection of retinal cells from oxidative-stress-induced apoptosis .....	481
Sulindac .....	481
Tandospirone .....	482
Cell therapy for macular degeneration .....	482
<i>Retinal pigment epithelial cells .....</i>	<i>482</i>
<i>Stem cells .....</i>	<i>482</i>
<i>Neural progenitor cells .....</i>	<i>482</i>
Gene therapy for retinal degeneration .....	483
RNAi-based treatments for AMD .....	483
<b>Neuroprotection in proliferative diabetic retinopathy .....</b>	<b>484</b>
RNAi-based approaches to diabetic retinopathy .....	484
<b>Clinical trials for optic nerve and retinal neuroprotection .....</b>	<b>485</b>
<b>13. Neuroprotection during Anesthesia and Surgery .....</b>	<b>487</b>
<b>Introduction .....</b>	<b>487</b>
<b>Anesthetic agents as neuroprotectives .....</b>	<b>487</b>
Barbiturates .....	487
<i>Thiopental .....</i>	<i>488</i>
Etomidate .....	489
Propofol .....	489
Ketamine .....	489
Gaseous anesthetics .....	490
<i>Isoflurane .....</i>	<i>490</i>
<i>Xenon .....</i>	<i>490</i>
Local anesthetics .....	491
<b>Monitoring of CNS function during anesthesia and surgery .....</b>	<b>491</b>
Monitoring of cerebral function .....	491
Monitoring of spinal cord function during spinal surgery .....	491
<b>Perioperative neuroprotection .....</b>	<b>492</b>
<b>Neuroprotection during cardiovascular procedures .....</b>	<b>493</b>
CNS complications of cardiac surgery .....	493
Neuroprotective strategies during cardiac surgery .....	494
<i>Neuroprotection before anticipated or induced cardiac arrest .....</i>	<i>495</i>
<i>Neuroprotection during coronary artery bypass grafting .....</i>	<i>495</i>
<i>Preconditioning with hyperbaric oxygen .....</i>	<i>496</i>
<i>Neuroprotection in aortic surgery .....</i>	<i>496</i>
<i>Pharmacologic strategies for neuroprotection in aortic surgery .....</i>	<i>497</i>
<b>Cerebral protection during organ transplantation surgery .....</b>	<b>497</b>
<b>Cerebral protection during neurosurgery .....</b>	<b>498</b>
Cerebral angiography and endovascular surgery .....	498
Cerebral protection during surgery for arteriovenous malformations .....	498
Cerebral protection during surgery of intracranial aneurysms .....	498
Management of subarachnoid hemorrhage .....	499
<i>Vasospasm associated with subarachnoid hemorrhage .....</i>	<i>499</i>
Cerebral protection during carotid endarterectomy .....	501
Cerebral protection during surgery of brain tumors .....	501
Neuroprotective measures prior to surgery .....	502
<i>HBO preconditioning for neuroprotection during surgery .....</i>	<i>502</i>
Neuroprotection following surgery .....	502
<i>Neuroprotection by cranioplasty after decompressive craniectomy .....</i>	<i>503</i>

<b>14. Markets for Neuroprotective Therapies.....</b>	<b>505</b>
<b>Introduction .....</b>	<b>505</b>
<b>The financial burden of CNS damage .....</b>	<b>505</b>
<b>Markets for neuroprotective therapies.....</b>	<b>505</b>
Markets according to therapeutic areas.....	505
Stroke .....	506
CNS injury .....	506
Alzheimer disease .....	507
Parkinson disease .....	507
Multiple sclerosis.....	507
Epilepsy.....	507
Values of neuroprotective therapies in major world markets.....	507
Unmet needs in neuroprotectives.....	508
<b>Future of neuroprotective therapies .....</b>	<b>509</b>
Challenges in neuroprotective drug development .....	509
Promising areas of research in neuroprotection.....	510
Autoreactive antibodies .....	510
Biological therapies for neuroprotection .....	510
Multidisciplinary approaches to neuroprotection .....	511
<b>15. References.....</b>	<b>513</b>

## Tables

Table 1-1: Historical landmarks in the development of neuroprotection .....	31
Table 1-2: Intrinsic neuroprotective factors.....	36
Table 1-3: Common features of pathophysiology of brain damage in diseases .....	44
Table 1-4: Place of neuroprotection in management of CNS disorders .....	45
Table 1-5: Indications for the use of neuroprotection .....	45
Table 1-6: Neuroprotective nanoparticles.....	51
Table 2-1: A classification of neuroprotective agents .....	55
Table 2-2: The neuroprotective effect of antiepileptic drugs .....	64
Table 2-3: Neuroprotective affect of minocycline in animal models.....	69
Table 2-4: Classification of antioxidants or free radical scavengers with neuroprotective potential.....	77
Table 2-5: Role of erythropoietin in the nervous system .....	82
Table 2-6: Ionotropic glutamate receptors .....	88
Table 2-7: Classification of metabotropic glutamate receptors (mGluRs) .....	88
Table 2-8: Methods for neuroprotection based on nonpharmacological preconditioning .....	140
Table 3-1: Cerebrovascular diseases that are relevant to neuroprotection.....	143
Table 3-2: Neuroprotective strategies for stroke .....	153
Table 3-3: Selected effective combinations of hypothermia with other neuroprotective strategies for the treatment of ischemic stroke in experimental models .....	184
Table 3-4: Neuroprotective gene transfer in models of cerebral ischemia .....	191
Table 3-5: Neuroprotective gene therapy in animal stroke models .....	191
Table 3-6: Neuroprotective agents in clinical development for acute cerebrovascular disease .....	194
Table 3-7: Some failed trials for neuroprotective therapy for stroke .....	197
Table 3-8: Preclinical assessment of neuroprotective agents in acute stroke models.....	206
Table 4-1: Classification of closed TBI .....	211
Table 4-2: Current conventional management of traumatic brain injury .....	220
Table 4-3: Neuroprotective strategies for traumatic brain injury .....	222
Table 4-4: Intrinsic factors that influence regeneration in the central nervous system .....	240
Table 4-5: A classification of approaches to regeneration of the brain following injury .....	241
Table 4-6: Ongoing or completed clinical trials for neuroprotection in TBI .....	243
Table 4-7: Discontinued or failed clinical trials for neuroprotection in TBI.....	244
Table 5-1: Secondary mechanisms in spinal cord injury.....	249
Table 5-2: Neuroprotective and regenerative approaches for SCI.....	250
Table 5-3: Clinical trials for neuroprotection in SCI .....	265
Table 6-1: Neurodegenerative disorders with dementia .....	275
Table 6-2: Drugs in clinical trials for spinal muscular atrophy .....	281
Table 6-3: Approaches to neuroprotection in CJD.....	283
Table 6-4: Glutamate-based therapies in clinical development for neurodegenerative disorders.....	285
Table 7-1: Prevalence of Parkinson's disease in major markets 2016-2026 .....	287
Table 7-2: Factors in the etiology of Parkinson's disease.....	287
Table 7-3: Strategies for the treatment of Parkinson's disease .....	295
Table 7-4: Gene therapy techniques applicable to Parkinson disease .....	308
Table 7-5: Current clinical trials of neuroprotective therapies for Parkinson disease .....	320
Table 7-6: Failed clinical trials of neuroprotective therapies for Parkinson disease.....	321
Table 7-7: Evaluation of neuroprotective agents for PD .....	322
Table 8-1: Cholinergic approaches to the treatment of Alzheimer's disease .....	327

Table 8-2: Neuroprotective agents for Alzheimer's disease.....	327
Table 8-3: Clinical trials for neuroprotection in Alzheimer disease .....	340
Table 8-4: Discontinued, failed or inconclusive clinical trials of Alzheimer disease .....	346
Table 8-5: Strategies for discovery of neuroprotective therapies for AD .....	349
Table 9-1: Neuroprotective approaches in HD.....	355
Table 10-1: Hypotheses for the pathogenesis of amyotrophic lateral sclerosis .....	367
Table 10-2: Genetic diagnostic biomarkers of ALS.....	370
Table 10-3: Classification of neuroprotective agents for amyotrophic lateral sclerosis.....	372
Table 10-4: Clinical trials of neuroprotective therapies for ALS .....	386
Table 10-5: Failed or discontinued trials of neuroprotective therapies for ALS.....	387
Table 11-1: Therapeutic approaches to subcortical vascular dementia .....	396
Table 11-2: Pharmacological neuroprotection against the sequelae of seizures .....	400
Table 11-3: Neuroprotective effect of AEDs in animal models of status epilepticus (SE).....	401
Table 11-4: Specific therapies for MS based on postulated pathomechanisms.....	407
Table 11-5: Approved neuroprotective therapies for multiple sclerosis.....	408
Table 11-6: Neuroprotective therapies for multiple sclerosis in clinical trials.....	409
Table 11-7: Measures to prevent acute bilirubin encephalopathy .....	438
Table 11-8: Approaches to neuroprotection in neonatal hypoxia-ischemia.....	445
Table 11-9: Drugs with neuroprotective effect at mitochondrial level.....	451
Table 11-10: Causes of sensorineural hearing impairment .....	455
Table 11-11: Strategies for prevention and treatment of sensorineural hearing loss.....	456
Table 11-12: Agents for neuroprotection of the peripheral nervous system .....	459
Table 12-1: Causes of optic neuropathy.....	465
Table 12-2: Clinical trials of neuroprotective therapies in optic neuritis.....	467
Table 12-3: Neuroprotection of the optic nerve in glaucoma.....	470
Table 12-4: Strategies for neuroprotection in retinal ischemia .....	473
Table 12-5: Novel neuroprotective strategies against retinal degeneration .....	478
Table 12-6: Clinical trials for retinal neuroprotection .....	485
Table 13-1: CNS complications associated with cardiac procedures .....	493
Table 13-2: Strategies for protection of the brain during cardiac surgery .....	494
Table 13-3: Medical and surgical methods of cerebral vasospasm management.....	500
Table 13-4: Neuroprotection by prevention of vasospasm.....	500
Table 14-1: Neuroprotective market values 2016-2026 .....	506
Table 14-2: Values of neuroprotective therapies in major world markets from 2016-26.....	507

## Figures

Figure 2-1: Mechanism of neuroprotective effect of sigma-1 receptor agonists .....	63
Figure 2-2: NMDA receptor ion channel complex.....	92
Figure 2-3: Neuroprotective effect of galantamine .....	114
Figure 3-1: Some steps in the ischemic cascade and site of action of neuroprotectives .....	144
Figure 3-2: Relationship between dementia and acute ischemic stroke .....	152
Figure 3-3: A roadmap for neuroprotection .....	207
Figure 4-1: Cascade of events following traumatic brain injury .....	213
Figure 4-2: Neurometabolic cascade of mild TBI .....	214
Figure 4-3: Secondary injury mechanisms after TBI .....	215
Figure 4-4: Management of raised ICP after TBI .....	221
Figure 5-1: Pathomechanism of acute spinal cord injury .....	248
Figure 7-1: Neuroprotective strategies against death of dopamine-containing neurons in PD .....	293
Figure 9-1: Role of HTT protein in pathogenesis of HD and points of intervention.....	362
Figure 9-2: Antisense therapeutic approaches to HD for lowering huntingtin .....	366
Figure 11-1: A schematic overview of synaptopathies.....	391
Figure 11-2: Common mechanisms of neural damage in cerebral ischemia and seizures.....	399
Figure 11-3: Role of neuroprotection in epilepsy and its treatment.....	400
Figure 11-4: Mechanisms of neonatal hypoxia-ischemia and targets for neuroprotection.....	444
Figure 14-1: Unmet therapeutic needs in neuroprotective therapies.....	509