

# **Neuroprotection**

## **Part I: Methods & Drugs**

**A Jain PharmaBiotech Report**



# **Neuroprotection**

## **Part I: Methods & Drugs**

**By**

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

**November 2018**

**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 478 publications include 30 books (6 as editor + 24 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 143 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, 3<sup>rd</sup> ed 2019 is in preparation) 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, 2<sup>nd</sup> edn 2019, in preparation), and "Applications of Biotechnology in Neurology" (Springer 2013). He has 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 2018 (first edition published in April 2000)  
Copyright © 2018 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>28</b> |
| <b>1. Introduction .....</b>                                                              | <b>32</b> |
| <b>Definitions .....</b>                                                                  | <b>32</b> |
| <b>Historical development of neuroprotection .....</b>                                    | <b>32</b> |
| <b>Neurophysiological basis of neuroprotection .....</b>                                  | <b>33</b> |
| Astrocytic glycogen-derived lactate as fuel for the brain.....                            | 33        |
| Gene expression in the human brain .....                                                  | 33        |
| Role of astrocytes in neuroprotection.....                                                | 34        |
| Role of glymphatic system in neuroprotection.....                                         | 34        |
| Role of sleep in neuroprotection.....                                                     | 35        |
| Role of cerebral metabolism in neuroprotection .....                                      | 35        |
| Role of circadian genes in neuroprotection .....                                          | 35        |
| Role of blood-brain barrier in neuroprotection.....                                       | 36        |
| Role of the gut microbiota in development of integrity of the BBB .....                   | 36        |
| <b>Intrinsic neuroprotective factors .....</b>                                            | <b>36</b> |
| Neuroprotective gene expression .....                                                     | 38        |
| <i>Upregulation of GADD34.....</i>                                                        | 38        |
| <i>Induction of NR4A proteins by CREB in neurons.....</i>                                 | 38        |
| <i>Elevation PGC-1<math>\alpha</math> for neuroprotection in PD.....</i>                  | 38        |
| Neurotrophic factors.....                                                                 | 39        |
| Intrinsic nonenzymatic antioxidants .....                                                 | 39        |
| Activation of transcription factor Nrf2 .....                                             | 39        |
| Intrinsic neuroprotective factors .....                                                   | 40        |
| <i><math>\alpha</math>B-crystallin.....</i>                                               | 40        |
| <i>Docosahexaenoic acid.....</i>                                                          | 40        |
| <i>Excitatory amino acid transporters.....</i>                                            | 40        |
| <i>Extracellular serine protease thrombin.....</i>                                        | 40        |
| <i>Galanin.....</i>                                                                       | 41        |
| <i>Neuroglobin .....</i>                                                                  | 41        |
| <i>Nuclear factor I-A .....</i>                                                           | 42        |
| <i>Prion protein .....</i>                                                                | 42        |
| <i>Rai adaptor protein .....</i>                                                          | 42        |
| Stem cell factor .....                                                                    | 42        |
| Role of the immune system in neuroprotection .....                                        | 43        |
| Induction of DNA repair enzymes for neuroprotection .....                                 | 43        |
| Microtubule-based neuroprotective response to axonal injury .....                         | 44        |
| <b>Pathomechanisms of CNS injury as basis for neuroprotection .....</b>                   | <b>44</b> |
| <b>Biomarkers of neurological disorders and neuroprotection.....</b>                      | <b>45</b> |
| CNS biomarker identification using proteomics .....                                       | 45        |
| Brain imaging for detection of biomarkers .....                                           | 46        |
| <b>Neuroprotection in neuroinflammation .....</b>                                         | <b>46</b> |
| Biomarkers of neuroinflammation .....                                                     | 46        |
| <b>Role of neuroprotection in various neurological disorders .....</b>                    | <b>47</b> |
| <b>Neuroprotection and neuroregeneration.....</b>                                         | <b>48</b> |
| <b>Acute versus chronic neuroprotection .....</b>                                         | <b>48</b> |
| <b>Discovery and evaluation of neuroprotective agents .....</b>                           | <b>49</b> |
| Neuroprotective drug discovery .....                                                      | 49        |
| Discovery of CNS drugs that penetrate the blood-brain barrier .....                       | 49        |
| In vitro assays for the evaluation of neuroprotective agents.....                         | 50        |
| Oxidative injury model to test neuroprotective drugs.....                                 | 50        |
| Apoptosis model for designing neuroprotective drugs .....                                 | 50        |
| Transgenic mouse models of neurological disorders.....                                    | 51        |
| Evaluating effects of neuroprotective drugs on living brain slices.....                   | 51        |
| Role of brain imaging in neuroprotective drug discovery and development .....             | 52        |
| <i>Positron emission tomography.....</i>                                                  | 52        |
| <i>Role of single photon emission computed tomography.....</i>                            | 52        |
| <i>Functional CT scanning to evaluate cerebrovascular protection .....</i>                | 53        |
| <i>Magnetic resonance imaging for the evaluation of neuroprotectives.....</i>             | 53        |
| Application of nanotechnology to neuroprotection .....                                    | 53        |
| <i>Nanoparticles as neuroprotective antioxidants .....</i>                                | 54        |
| <i>Cadmium telluride nanoparticles prevent A<math>\beta</math> fibril formation .....</i> | 55        |
| Evaluation criteria for potential neuroprotective agents.....                             | 55        |
| <b>2. Neuroprotective Agents .....</b>                                                    | <b>56</b> |
| <b>Classification of neuroprotective agents .....</b>                                     | <b>56</b> |
| <b><math>\alpha</math>2 adrenoceptor agonists .....</b>                                   | <b>60</b> |

|                                                                                |           |
|--------------------------------------------------------------------------------|-----------|
| Dexmedetomidine .....                                                          | 60        |
| <b>Activated protein C .....</b>                                               | <b>61</b> |
| <b>Activity-dependent neuroprotective protein .....</b>                        | <b>61</b> |
| Davunetide .....                                                               | 61        |
| <b>Adenosine analogs .....</b>                                                 | <b>62</b> |
| Propentofylline .....                                                          | 62        |
| <b>Antidepressants .....</b>                                                   | <b>62</b> |
| Antidepressant-induced neurogenesis .....                                      | 62        |
| Neurogenesis induced by electroconvulsive therapy .....                        | 63        |
| Neuroprotective effect of selective serotonin reuptake inhibitors .....        | 63        |
| <i>Fluoxetine as a neuroprotective agent</i> .....                             | 65        |
| <b>Antiepileptic drugs as neuroprotectives .....</b>                           | <b>65</b> |
| BIS-001 .....                                                                  | 66        |
| Levetiracetam .....                                                            | 66        |
| Phenytoin .....                                                                | 67        |
| Valproic acid .....                                                            | 67        |
| <b>Antiinflammatory agents .....</b>                                           | <b>67</b> |
| Aspirin .....                                                                  | 68        |
| Interleukin-1 antagonists .....                                                | 68        |
| COX-2 inhibitors .....                                                         | 69        |
| <i>Nimesulide</i> .....                                                        | 69        |
| Gold microparticles as anti-neuroinflammatory agents .....                     | 69        |
| Minocycline .....                                                              | 69        |
| Prostaglandin receptor antagonists .....                                       | 70        |
| <b>Anti-apoptosis agents .....</b>                                             | <b>71</b> |
| Activated protein C .....                                                      | 72        |
| Calpain inhibitors .....                                                       | 72        |
| Caspase inhibitors .....                                                       | 72        |
| DNA binding drugs .....                                                        | 72        |
| Lithium .....                                                                  | 73        |
| Melatonin .....                                                                | 73        |
| Olesoxime .....                                                                | 73        |
| Omega-3 fatty acids .....                                                      | 74        |
| <i>Docosahexaenoic acid</i> .....                                              | 74        |
| Poly(ADP-ribose) polymerase inhibitors .....                                   | 74        |
| Prevention of apoptosis by binding of proNGF to sortilin .....                 | 75        |
| <b>Antioxidants/free radical scavengers .....</b>                              | <b>76</b> |
| Free radical generation .....                                                  | 76        |
| Natural defenses against oxidative stress .....                                | 76        |
| Effects of oxidative damage .....                                              | 76        |
| <i>Oxidative damage and aging</i> .....                                        | 76        |
| <i>Neuronal damage by free radicals</i> .....                                  | 77        |
| <i>Oxidative damage and neurodegenerative disorders</i> .....                  | 77        |
| Measures to control oxidative stress .....                                     | 78        |
| <i>Categories of therapeutic antioxidants</i> .....                            | 78        |
| <i>Alpha-phenyl-tert-butyl nitron</i> .....                                    | 79        |
| <i>Coenzyme Q10</i> .....                                                      | 79        |
| <i>Dihydroergocryptine</i> .....                                               | 79        |
| <i>Flavonoids</i> .....                                                        | 80        |
| <i>Mitochondria-targeted antioxidants</i> .....                                | 80        |
| <i>Neuroleptics as antioxidants</i> .....                                      | 80        |
| <i>Nitrones</i> .....                                                          | 80        |
| <i>NRF2 for augmenting neuroprotection against oxidative stress</i> .....      | 81        |
| Translation of antioxidant neuroprotection from preclinical to clinical .....  | 81        |
| <b>Carbon monoxide and heme oxygenase .....</b>                                | <b>82</b> |
| <b>Cell transplants .....</b>                                                  | <b>82</b> |
| Cells secreting neuroprotective substances .....                               | 82        |
| Stem cells .....                                                               | 83        |
| Stem cell activation for neuroprotection/regeneration by glucocorticoids ..... | 83        |
| Use of neural stem cells to construct the blood brain barrier .....            | 83        |
| <b>Cytokines .....</b>                                                         | <b>83</b> |
| Erythropoietin .....                                                           | 83        |
| <i>Non-erythropoietic EPO variants and mimics</i> .....                        | 85        |
| Granulocyte colony-stimulating factor .....                                    | 86        |
| <b>Delta-opioid receptor agonists .....</b>                                    | <b>86</b> |
| Delta opioid peptide-induced hibernation for neuroprotection .....             | 86        |
| <b>FK960 .....</b>                                                             | <b>86</b> |
| <b>Gene therapy .....</b>                                                      | <b>87</b> |
| <b>Glucagon-like peptide .....</b>                                             | <b>88</b> |
| <b>Glatiramer acetate .....</b>                                                | <b>88</b> |
| <b>Glutamate antagonists .....</b>                                             | <b>88</b> |

|                                                                               |            |
|-------------------------------------------------------------------------------|------------|
| Neuroprotection by scavenging blood glutamate .....                           | 89         |
| N-acylethanolamines for protection against glutamatergic excitotoxicity ..... | 90         |
| Glutamate transporters.....                                                   | 90         |
| Glutamate transporter-mediated neuroprotective effect of drugs.....           | 90         |
| Neuroprotection by targeting KAI subunit of kainate receptor .....            | 91         |
| <b>Glycine-proline-glutamate analogs .....</b>                                | <b>92</b>  |
| <b>Hydrogen sulfide.....</b>                                                  | <b>92</b>  |
| Hibernation induced by hydrogen sulfide.....                                  | 92         |
| <b>NMDA receptor ion channel complex.....</b>                                 | <b>92</b>  |
| NMDA receptor antagonists .....                                               | 95         |
| <i>NMDA NR2B subunit receptor antagonists</i> .....                           | 95         |
| <i>Ifenprodil</i> .....                                                       | 95         |
| <i>Memantine as a neuroprotective agent</i> .....                             | 95         |
| <i>NAALADase inhibitors</i> .....                                             | 96         |
| <i>Gacyclidine</i> .....                                                      | 96         |
| <i>N-alkylglycines</i> .....                                                  | 96         |
| AMPA receptor modulators .....                                                | 96         |
| Metabotropic glutamate receptor modulators.....                               | 97         |
| Cannabinoids.....                                                             | 97         |
| Dexanabinol .....                                                             | 98         |
| <b>Glutathione.....</b>                                                       | <b>98</b>  |
| <b>Heat shock proteins .....</b>                                              | <b>98</b>  |
| <b>Histone deacetylase inhibitors for neuroprotection .....</b>               | <b>99</b>  |
| <b>Hormones .....</b>                                                         | <b>99</b>  |
| Estrogen and neuroprotection.....                                             | 99         |
| <i>Neuroprotective effect of estrogen receptor ligands</i> .....              | 100        |
| <i>Selective estrogen receptor modulators</i> .....                           | 100        |
| <i>Mitochondrial mechanisms of estrogen neuroprotection</i> .....             | 101        |
| Insulin.....                                                                  | 101        |
| <b>Ion Channel modulators .....</b>                                           | <b>102</b> |
| Calcium channel blockers.....                                                 | 102        |
| <i>Ziconotide</i> .....                                                       | 102        |
| Na <sup>+</sup> channel blockers.....                                         | 103        |
| Neuroprotective potassium channel inhibitors.....                             | 103        |
| <b>Kynurenine inhibitors .....</b>                                            | <b>104</b> |
| <b>Leukocyte adhesion inhibitors .....</b>                                    | <b>104</b> |
| <b>Modafinil.....</b>                                                         | <b>105</b> |
| <b>Neural regeneration protein .....</b>                                      | <b>105</b> |
| <b>Neurite outgrowth-promoting agents .....</b>                               | <b>105</b> |
| Prostaglandin compounds .....                                                 | 105        |
| Monoclonal antibodies .....                                                   | 106        |
| <b>Neuroimmunophilins.....</b>                                                | <b>106</b> |
| Cyclosporin-A .....                                                           | 106        |
| FK506 .....                                                                   | 107        |
| Rapamycin.....                                                                | 107        |
| <b>Neurotrophic factors.....</b>                                              | <b>108</b> |
| Activity-dependent neurotrophic factor .....                                  | 108        |
| Bone morphogenetic proteins .....                                             | 108        |
| Brain-derived neurotrophic factor.....                                        | 109        |
| Ciliary neurotrophic factor.....                                              | 109        |
| Fibroblast growth factors .....                                               | 110        |
| Glial cell line-derived neurotrophic factor .....                             | 110        |
| Insulin-like growth factor .....                                              | 111        |
| Nerve growth factor .....                                                     | 111        |
| Neurotrophins .....                                                           | 112        |
| Osteogenic protein-1 .....                                                    | 112        |
| Pigment epithelium-derived factor.....                                        | 112        |
| Transforming growth factor-β1 .....                                           | 113        |
| Vascular endothelial growth factor .....                                      | 113        |
| Neurotrophic factor-related neuroprotective agents.....                       | 113        |
| <i>Amitriptyline as a TrkA and TrkB receptor agonist</i> .....                | 113        |
| <i>Colivelin</i> .....                                                        | 113        |
| <i>Gambogic amide</i> .....                                                   | 114        |
| <i>Inosine</i> .....                                                          | 114        |
| <i>Meteorin</i> .....                                                         | 114        |
| <i>Oxygen-regulated protein 150 kD</i> .....                                  | 115        |
| <i>Prosaptide</i> .....                                                       | 115        |
| <i>Siagoside</i> .....                                                        | 115        |
| <i>Small molecule activators of the Trk receptors</i> .....                   | 115        |
| <b>Nicotine and nicotinic receptor agonists .....</b>                         | <b>116</b> |
| <i>Neuroprotective effect of galantamine mediated via α7nAChRs</i> .....      | 116        |

|                                                                                               |            |
|-----------------------------------------------------------------------------------------------|------------|
| <i>Galantamine-induced A<math>\beta</math> clearance via <math>\alpha</math>7nAChRs</i> ..... | 117        |
| <b>Nitric oxide-based neuroprotection</b> .....                                               | <b>117</b> |
| Nitric oxide synthase inhibitors .....                                                        | 118        |
| Nitric oxide mimetics .....                                                                   | 118        |
| Nitric oxide donating derivatives .....                                                       | 118        |
| <b>Nootropics</b> .....                                                                       | <b>119</b> |
| <i>Piracetam</i> .....                                                                        | 119        |
| <b>Nutraceuticals and naturally-derived compounds</b> .....                                   | <b>120</b> |
| Cinnamon .....                                                                                | 120        |
| Coffee .....                                                                                  | 120        |
| Creatine .....                                                                                | 121        |
| Curcumin/curry .....                                                                          | 121        |
| <i>Mechanism of neuroprotective effect of curcumin</i> .....                                  | 122        |
| Flavonoids .....                                                                              | 122        |
| Glyceryltriacetate .....                                                                      | 122        |
| Green tea .....                                                                               | 122        |
| Herbal preparations .....                                                                     | 123        |
| <i>Flavonoid wogonin</i> .....                                                                | 123        |
| <i>Ginseng</i> .....                                                                          | 123        |
| Nicotinamide .....                                                                            | 123        |
| Punicalagin from pomegranate .....                                                            | 124        |
| Resveratrol .....                                                                             | 124        |
| <b>Osmotic diuretics</b> .....                                                                | <b>125</b> |
| Mannitol .....                                                                                | 125        |
| Osteopontin .....                                                                             | 125        |
| <b>Oxygen therapeutics</b> .....                                                              | <b>126</b> |
| Oxygen carriers .....                                                                         | 126        |
| Hemoglobin-based oxygen carriers .....                                                        | 126        |
| Perfluorocarbons as oxygen carriers .....                                                     | 127        |
| Hyperbaric oxygen therapy .....                                                               | 128        |
| <b>P7C3 compounds</b> .....                                                                   | <b>128</b> |
| <b>Peptides</b> .....                                                                         | <b>128</b> |
| C3-derived peptide for neuroprotection and neuroregeneration .....                            | 128        |
| Corticotropin-releasing hormone .....                                                         | 129        |
| Thyrotropin-releasing hormone .....                                                           | 129        |
| Vasoactive intestinal peptide .....                                                           | 129        |
| <b>Pharmacological preconditioning</b> .....                                                  | <b>130</b> |
| <b>PPARs as drug targets for neuroprotection</b> .....                                        | <b>130</b> |
| <b>Proteins</b> .....                                                                         | <b>131</b> |
| Amyloid precursor protein .....                                                               | 131        |
| Protein kinase C activators .....                                                             | 131        |
| <b>Riluzole</b> .....                                                                         | <b>131</b> |
| <b>Role of RNA interference in neuroprotection</b> .....                                      | <b>132</b> |
| Role of miRNA in neuroprotection .....                                                        | 132        |
| <b>Sigma receptor agonists as neuroprotective agents</b> .....                                | <b>132</b> |
| <b>SIRT group of proteins</b> .....                                                           | <b>133</b> |
| <b>Statins</b> .....                                                                          | <b>133</b> |
| <b>Steroids</b> .....                                                                         | <b>134</b> |
| Dehydroepiandrosterone .....                                                                  | 135        |
| HF0220 .....                                                                                  | 135        |
| <b>Sulforaphane</b> .....                                                                     | <b>135</b> |
| <b>Tauroursodeoxycholic acid</b> .....                                                        | <b>136</b> |
| <b>Tetanus toxin as a neuroprotective agent</b> .....                                         | <b>136</b> |
| <b>Thrombolytic agents as neuroprotective agents</b> .....                                    | <b>136</b> |
| <b>Uncoupling protein 2</b> .....                                                             | <b>137</b> |
| <b>Vaccines as neuroprotectives</b> .....                                                     | <b>137</b> |
| <b>Vitamins as neuroprotective agents</b> .....                                               | <b>137</b> |
| Vitamin B12 .....                                                                             | 137        |
| Vitamin D .....                                                                               | 138        |
| <b>Unconventional biologicals</b> .....                                                       | <b>138</b> |
| <b>Non-pharmacological approaches to neuroprotection</b> .....                                | <b>138</b> |
| Caloric restriction .....                                                                     | 139        |
| Cerebral exercise .....                                                                       | 139        |
| <i>Bilingualism for prevention of decline of mental function</i> .....                        | 139        |
| Electrical fields for improvement of cerebral function in neurodegeneration .....             | 139        |
| Environmental enrichment .....                                                                | 140        |
| Hypothermia .....                                                                             | 140        |
| <i>Limitations of hypothermia</i> .....                                                       | 141        |
| <i>Hypothermic neuroprotection in hypoxia-ischemia</i> .....                                  | 141        |
| Ketogenic diet .....                                                                          | 142        |
| Mediterranean diet .....                                                                      | 142        |



|                                                                               |            |
|-------------------------------------------------------------------------------|------------|
| Nonpharmacological preconditioning for neuroprotection.....                   | 142        |
| Physical exercise.....                                                        | 143        |
| Suspended animation and neuroprotection.....                                  | 144        |
| Transcranial magnetic stimulation.....                                        | 144        |
| <b>3. Neuroprotection in Cerebrovascular Disease.....</b>                     | <b>146</b> |
| <b>Introduction.....</b>                                                      | <b>146</b> |
| <b>Pathophysiology of cerebral ischemia.....</b>                              | <b>147</b> |
| Calcium overload.....                                                         | 147        |
| Ion channel dysfunction in stroke.....                                        | 147        |
| Role of oxygen free radicals in cerebral ischemia.....                        | 148        |
| Role of nitric oxide in cerebral ischemia.....                                | 148        |
| Glutamate as a biomarker of stroke.....                                       | 148        |
| Cerebral edema in stroke.....                                                 | 148        |
| Gene expression in response to cerebral ischemia.....                         | 149        |
| Induction of heat shock proteins in stroke.....                               | 149        |
| Role of cytokines and adhesion molecules in stroke.....                       | 149        |
| <i>Tumor necrosis factor-<math>\alpha</math></i> .....                        | 150        |
| <i>Interleukin-1 and IL-6</i> .....                                           | 150        |
| <i>Adhesion molecules</i> .....                                               | 150        |
| DNA damage and repair in cerebral ischemia.....                               | 150        |
| Role of neurotrophic factors in stroke.....                                   | 151        |
| <i>Problems requiring investigation of the role of NTFs in stroke</i> .....   | 151        |
| Role of Poly(ADP-ribose) polymerase (PARP) gene.....                          | 151        |
| Role of protease-activated receptor 1.....                                    | 152        |
| <b>Reperfusion injury after cerebral ischemia.....</b>                        | <b>152</b> |
| <b>Neuroprotection according to zones in cerebral infarction.....</b>         | <b>152</b> |
| Zone of ischemic infarction.....                                              | 152        |
| Penumbra.....                                                                 | 153        |
| <b>Current management of stroke.....</b>                                      | <b>153</b> |
| Neuroprotection in stenosis of intracranial arteries.....                     | 154        |
| Neuroprotection in stroke with intracerebral hemorrhage.....                  | 154        |
| Neuroprotection in cerebrovascular malformations.....                         | 154        |
| <i>Arteriovenous malformations</i> .....                                      | 154        |
| <i>Cavernous cerebrovascular malformations</i> .....                          | 155        |
| Neuroprotective strategies for ischemic stroke in patients with dementia..... | 155        |
| Neuroprotection in transient ischemic attacks.....                            | 156        |
| Secondary prevention of stroke.....                                           | 156        |
| <b>Neuroprotective therapies for stroke.....</b>                              | <b>156</b> |
| <b>Pharmacologic neuroprotective agents for stroke.....</b>                   | <b>158</b> |
| $\alpha$ B-crystallin as a neuroprotectant in stroke.....                     | 158        |
| Acid-sensing ion channel blockers.....                                        | 158        |
| AMPA receptor antagonists as neuroprotectives for stroke.....                 | 158        |
| <i>Zonampanel</i> .....                                                       | 158        |
| Antiapoptotic neuroprotectives.....                                           | 159        |
| <i>NIM811</i> .....                                                           | 159        |
| <i>Creatine as neuroprotective in stroke</i> .....                            | 159        |
| <i>Lithium as a neuroprotective in stroke</i> .....                           | 159        |
| <i>TUDCA as a neuroprotective in stroke</i> .....                             | 159        |
| Antiepileptic drugs as neuroprotectives in stroke.....                        | 160        |
| <i>Tiagabine</i> .....                                                        | 160        |
| <i>Topiramate</i> .....                                                       | 160        |
| <i>Zonisamide</i> .....                                                       | 160        |
| Anti-HMGB1 monoclonal antibody.....                                           | 161        |
| Antioxidant approaches.....                                                   | 161        |
| <i>Carnosine as a neuroprotective in stroke</i> .....                         | 161        |
| <i>Dehydroascorbic acid</i> .....                                             | 162        |
| <i>Tocotrienols</i> .....                                                     | 162        |
| <i>Uric acid</i> .....                                                        | 163        |
| Antiglutamate compounds.....                                                  | 163        |
| <i>MRZ 2/576</i> .....                                                        | 163        |
| <i>L-Phenylalanine</i> .....                                                  | 163        |
| Arimoclomol for stroke.....                                                   | 164        |
| Cardiac glycosides as neuroprotectives in stroke.....                         | 164        |
| Clenbuterol.....                                                              | 164        |
| Coagulation inhibitors as neuroprotectives.....                               | 164        |
| <i>Heparin and enoxaparin</i> .....                                           | 164        |
| <i>Warfarin vs dabigatran</i> .....                                           | 165        |
| <i>Apixaban</i> .....                                                         | 165        |
| Cox-2 inhibitors for ischemic stroke.....                                     | 165        |
| Curcumin as a neuroprotectant in stroke.....                                  | 166        |

|                                                                               |            |
|-------------------------------------------------------------------------------|------------|
| Docosahexaenoic acid for ischemic stroke .....                                | 166        |
| Ephrin-A5 blockers .....                                                      | 166        |
| Estrogen for stroke .....                                                     | 167        |
| Extendin-4 .....                                                              | 168        |
| Flavones for neuroprotection in stroke .....                                  | 168        |
| <i>Epicatechin</i> .....                                                      | 168        |
| <i>Isorhamnetin</i> .....                                                     | 169        |
| Granulocyte-macrophage colony-stimulating factor for cerebral ischemia .....  | 169        |
| Hamartin induction by cerebral ischemia as a basis for neuroprotection .....  | 169        |
| Histone deacetylase inhibitors for neuroprotection in stroke .....            | 170        |
| Histamine H <sub>2</sub> -receptor modulation .....                           | 170        |
| Inosine for stroke .....                                                      | 170        |
| Insulin-like growth factor-I .....                                            | 170        |
| Intravenous immunoglobulin as neuroprotective in stroke .....                 | 171        |
| Ischemic preconditioning for neuroprotection in stroke .....                  | 171        |
| Ketone bodies for neuroprotection in stroke .....                             | 172        |
| Magnesium .....                                                               | 172        |
| Mineralocorticoid receptor blockade for neuroprotection .....                 | 172        |
| miR-223 and neuroprotection in stroke .....                                   | 173        |
| Multifunctional neuroprotective agents .....                                  | 173        |
| NA-1 as neuroprotective against ischemic stroke .....                         | 173        |
| Nasal delivery of neuroprotective agents in stroke .....                      | 173        |
| Neuroserpin as a neuroprotective in stroke .....                              | 174        |
| N-2-mercaptopropionyl glycine .....                                           | 174        |
| NeuroAid .....                                                                | 174        |
| Neurotrophic factors as neuroprotectives for stroke .....                     | 175        |
| <i>Brain-derived neurotrophic factor</i> .....                                | 175        |
| <i>Fibroblast growth factor</i> .....                                         | 175        |
| <i>G-CSF</i> .....                                                            | 176        |
| <i>Glial cell line-derived neurotrophic factor</i> .....                      | 176        |
| <i>Insulin-like growth factor-1</i> .....                                     | 176        |
| <i>Neuregulin-1</i> .....                                                     | 176        |
| NO-based strategies for neuroprotection in cerebral ischemia .....            | 177        |
| NOX-4 inhibitors for neuroprotection in stroke .....                          | 177        |
| Omega-3 fatty acids for neuroprotection after cerebral ischemia-hypoxia ..... | 177        |
| Pannexin channel blockers for neuroprotection in stroke .....                 | 178        |
| Perlecan domain V .....                                                       | 178        |
| Peroxisome proliferator-activated receptor- $\gamma$ agonists .....           | 178        |
| PGE <sub>2</sub> EP2 receptor activation .....                                | 178        |
| Pioglitazone for reduction of stroke risk .....                               | 179        |
| Progesterone .....                                                            | 179        |
| Propofol as neuroprotective in stroke .....                                   | 179        |
| Proteoglycan-degrading enzymes .....                                          | 179        |
| Proteasome inhibitors .....                                                   | 180        |
| Statins for prevention and neuroprotection in stroke .....                    | 180        |
| Sildenafil .....                                                              | 181        |
| Src receptor blockade .....                                                   | 181        |
| Stroke vaccine .....                                                          | 181        |
| SUN N4057 .....                                                               | 182        |
| Thrombosis inhibitors .....                                                   | 182        |
| <i>Aspirin</i> .....                                                          | 182        |
| <i>Clopidogrel</i> .....                                                      | 183        |
| <i>Dipyridamole</i> .....                                                     | 183        |
| <i>Ticagrelor</i> .....                                                       | 183        |
| Vitamin E for neuroprotection in stroke .....                                 | 183        |
| <b>Neuroprotection in ischemia-reperfusion injury .....</b>                   | <b>184</b> |
| Aminoguanidine .....                                                          | 184        |
| Dexmedetomidine .....                                                         | 184        |
| Methylene blue for neuroprotection in ischemia-reperfusion injury .....       | 185        |
| Miscellaneous agents for neuroprotection in reperfusion injury .....          | 185        |
| <b>Neuroprotection by treatment of cerebrovascular malformations .....</b>    | <b>185</b> |
| <i>Arteriovenous malformations</i> .....                                      | 185        |
| <i>Cerebral cavernous malformations</i> .....                                 | 186        |
| <b>Prevention of hemorrhage following ischemic stroke .....</b>               | <b>186</b> |
| <b>Non-pharmacological neuroprotective therapies for stroke .....</b>         | <b>186</b> |
| Hypothermia for neuroprotection in acute stroke .....                         | 186        |
| Hyperbaric oxygen therapy for neuroprotection in acute stroke .....           | 187        |
| Hypothermia combination with other neuroprotective strategies .....           | 188        |
| Infrared laser therapy for ischemic stroke .....                              | 189        |
| Preconditioning for neuroprotection against cerebral ischemia .....           | 189        |
| <i>Neuroprotection in ischemia/reperfusion injury</i> .....                   | 189        |

|                                                                                |            |
|--------------------------------------------------------------------------------|------------|
| <b>Neurosurgical procedures for stroke.....</b>                                | <b>190</b> |
| Neurosurgical procedures for neuroprotection in acute stroke .....             | 190        |
| <i>Decompressive hemicraniectomy</i> .....                                     | 190        |
| <i>Thrombectomy</i> .....                                                      | 191        |
| <i>Stenting</i> .....                                                          | 191        |
| <i>Multiple endovascular modalities</i> .....                                  | 192        |
| Neurosurgical procedures for chronic cerebral ischemia .....                   | 193        |
| Neurostimulation of sphenopalatine ganglion.....                               | 193        |
| Stent versus surgery for asymptomatic carotid stenosis.....                    | 193        |
| <b>Neurorehabilitation in relation to neuroprotection in stroke.....</b>       | <b>194</b> |
| Protective effect of physical activity on stroke in the elderly .....          | 194        |
| <b>Biological therapies for stroke .....</b>                                   | <b>194</b> |
| Cell therapy for stroke .....                                                  | 194        |
| <i>Stem cell transplant for stroke</i> .....                                   | 194        |
| <i>Immortalized cell grafts for stroke</i> .....                               | 195        |
| <i>Stimulation of intrinsic stem cells for repair of brain in stroke</i> ..... | 195        |
| Gene therapy for neuroprotection in cerebrovascular disease .....              | 195        |
| Regulation of microRNAs for neuroprotection in cerebral ischemia .....         | 197        |
| RNAi-based therapy for neuroprotection in stroke .....                         | 198        |
| Vaccines for neuroprotection in stroke .....                                   | 198        |
| <b>Neuroprotective therapies for cerebral ischemia: clinical trials .....</b>  | <b>198</b> |
| Albumin .....                                                                  | 199        |
| Free radical scavengers .....                                                  | 199        |
| DP-b99 .....                                                                   | 201        |
| Mildronate.....                                                                | 201        |
| Minocycline for neuroprotection in stroke .....                                | 201        |
| Perindopril .....                                                              | 202        |
| Failed clinical trials of neuroprotection in stroke.....                       | 202        |
| <i>Ancrod</i> .....                                                            | 203        |
| <i>Aptiganel</i> .....                                                         | 204        |
| <i>Cerovive</i> .....                                                          | 204        |
| <i>Citicoline</i> .....                                                        | 205        |
| <i>Desmoteplase</i> .....                                                      | 206        |
| <i>Erythropoietin as a neuroprotective in stroke</i> .....                     | 207        |
| <i>SPD 502</i> .....                                                           | 207        |
| <i>Tirilazad mesylate</i> .....                                                | 207        |
| <i>Selfotel</i> .....                                                          | 207        |
| <i>Lubeluzole</i> .....                                                        | 207        |
| <i>Nalmefene</i> .....                                                         | 208        |
| <i>Gavestinel</i> .....                                                        | 208        |
| <i>Nimodipine</i> .....                                                        | 208        |
| <i>Sipatrigine</i> .....                                                       | 209        |
| <i>Causes of failure of stroke trials</i> .....                                | 209        |
| Measures for prevention of failures in stroke trials .....                     | 210        |
| Design of acute stroke trial to facilitate drug approval .....                 | 212        |
| <b>The ideal neuroprotective agent for stroke .....</b>                        | <b>212</b> |
| <b>Prevention of stroke .....</b>                                              | <b>213</b> |
| <b>Future of neuroprotection in stroke .....</b>                               | <b>213</b> |
| <br>                                                                           |            |
| <b>4. Neuroprotection in Traumatic Brain Injury .....</b>                      | <b>216</b> |
| <b>Introduction .....</b>                                                      | <b>216</b> |
| <b>Cerebral hypoxia/ischemia as a complication of trauma.....</b>              | <b>216</b> |
| <b>Epidemiology of TBI.....</b>                                                | <b>216</b> |
| TBI in the military .....                                                      | 217        |
| <b>Pathophysiology of TBI.....</b>                                             | <b>217</b> |
| Immediate damage following TBI.....                                            | 218        |
| Cerebral edema following TBI.....                                              | 218        |
| Neurometabolic cascade after TBI .....                                         | 219        |
| Delayed damage following TBI.....                                              | 219        |
| Mechanism of axonal damage after TBI .....                                     | 220        |
| Role of neuroinflammation in TBI .....                                         | 220        |
| BBB damage after TBI .....                                                     | 220        |
| Molecular events following TBI.....                                            | 221        |
| Chronic traumatic encephalopathy .....                                         | 221        |
| Neurocognitive sequelae of TBI.....                                            | 223        |
| Changes in neurotrophic factors following TBI .....                            | 223        |
| Changes in neurotransmitters following TBI.....                                | 223        |
| Proteomics of TBI .....                                                        | 224        |
| Genetic influences on outcome following TBI .....                              | 224        |
| <b>Management of TBI .....</b>                                                 | <b>225</b> |
| Management during acute phase of head injury .....                             | 225        |

|                                                                                      |            |
|--------------------------------------------------------------------------------------|------------|
| <i>Control of intracranial pressure and cerebral edema</i> .....                     | 225        |
| <i>Corticosteroids</i> .....                                                         | 226        |
| <i>Decompressive craniectomy</i> .....                                               | 227        |
| <b>Neuroprotection in TBI</b> .....                                                  | <b>227</b> |
| Amantadine.....                                                                      | 228        |
| Antioxidants .....                                                                   | 229        |
| Barbiturates .....                                                                   | 229        |
| $\beta$ - and $\gamma$ -secretase inhibitors .....                                   | 229        |
| Beta blockers .....                                                                  | 229        |
| Bradykinin B <sub>2</sub> antagonists .....                                          | 230        |
| Cell cycle inhibitors for TBI.....                                                   | 230        |
| COX-2 inhibitors for neuroprotection in TBI .....                                    | 230        |
| Cyclosporin for neuroprotection in TBI .....                                         | 231        |
| Dexanabinol for TBI .....                                                            | 231        |
| Erythropoietin for neuroprotection in TBI .....                                      | 231        |
| Gold implants for neuroprotection in focal TBI .....                                 | 232        |
| Histone deacetylase inhibitors for neuroprotection in TBI .....                      | 232        |
| KN 38-7271 .....                                                                     | 232        |
| Levosimendan .....                                                                   | 232        |
| Magnesium sulfate .....                                                              | 233        |
| Minocycline for TBI.....                                                             | 233        |
| Multipotential neuroprotective agents for TBI .....                                  | 233        |
| Nutritional approaches to neuroprotection in TBI.....                                | 233        |
| <i>Branched chain amino acids to ameliorate cognitive impairment in TBI</i> .....    | 234        |
| <i>Creatine for neuroprotection in TBI</i> .....                                     | 234        |
| <i>Nicotinamide for neuroprotection in TBI</i> .....                                 | 235        |
| <i>Omega 3 fatty acids as neuroprotectives in TBI</i> .....                          | 235        |
| Neurotrophic factors for TBI .....                                                   | 235        |
| Neurosteroids as neuroprotective agents for TBI.....                                 | 236        |
| NMDA receptor antagonists .....                                                      | 237        |
| <i>Neuroprotection in TBI against glutamate-induced excitotoxicity</i> .....         | 237        |
| <i>NP-1</i> .....                                                                    | 238        |
| Nogo-A inhibitor .....                                                               | 238        |
| Oxygen carriers for TBI.....                                                         | 238        |
| Polyethylene glycol for neuroprotection in TBI .....                                 | 239        |
| Propofol for neuroprotection in TBI.....                                             | 239        |
| Rapamycin as neuroprotective in TBI.....                                             | 239        |
| Simvastatin as neuroprotective in TBI .....                                          | 240        |
| Targeting mitochondrial pathology in TBI .....                                       | 240        |
| Thyrotropin-releasing hormone analogs .....                                          | 240        |
| Tissue plasminogen activator.....                                                    | 240        |
| Traxoprodil .....                                                                    | 241        |
| <b>Biological approaches to neuroprotection in TBI</b> .....                         | <b>241</b> |
| Antisense approaches to TBI .....                                                    | 241        |
| Cell therapy for TBI.....                                                            | 241        |
| Gene therapy for TBI.....                                                            | 242        |
| Vaccines for TBI.....                                                                | 242        |
| <b>Non-pharmaceutical approaches to neuroprotection in TBI</b> .....                 | <b>242</b> |
| Deep brain stimulation for TBI.....                                                  | 242        |
| Hyperbaric oxygen therapy for TBI.....                                               | 243        |
| Hypothermia .....                                                                    | 243        |
| Reduction of microglial migration after TBI.....                                     | 243        |
| Vacuum for mechanical tissue resuscitation in TBI .....                              | 244        |
| <b>Prophylactic neuroprotection against TBI</b> .....                                | <b>244</b> |
| Role of helmets in protection against TBI .....                                      | 244        |
| Role of physical exercise in protection against TBI .....                            | 244        |
| <b>Neuroprotection against late sequelae of TBI</b> .....                            | <b>245</b> |
| Antiepileptic drugs for prevention of seizures and neuroprotection .....             | 245        |
| <b>Neuroprotection during rehabilitation phase of TBI</b> .....                      | <b>245</b> |
| Neuroregeneration following TBI .....                                                | 246        |
| <i>Intrinsic factors that influence regeneration following TBI</i> .....             | 246        |
| <i>Causes of lack of regeneration following TBI</i> .....                            | 246        |
| <i>Approaches to regeneration of the brain following TBI</i> .....                   | 246        |
| <b>Clinical trials of neuroprotective agents in TBI</b> .....                        | <b>248</b> |
| Ongoing clinical trials in TBI .....                                                 | 248        |
| Failed clinical trials in TBI.....                                                   | 249        |
| <i>Differences between clinical trials and studies in animal models of TBI</i> ..... | 250        |
| <i>Subgroup analysis</i> .....                                                       | 250        |
| <i>Improving the clinical trial design</i> .....                                     | 250        |
| <i>Clinical trials combining multiple treatment strategies</i> .....                 | 251        |
| <i>Shortening the trial time</i> .....                                               | 251        |

|                                                                                  |            |
|----------------------------------------------------------------------------------|------------|
| <b>Conclusions and future prospects of neuroprotection in TBI.....</b>           | <b>251</b> |
| <b>5. Neuroprotection in Spinal Cord Injury .....</b>                            | <b>253</b> |
| <b>Introduction .....</b>                                                        | <b>253</b> |
| <b>Pathophysiology of SCI.....</b>                                               | <b>253</b> |
| .....                                                                            | 254        |
| <i>Secondary mechanisms of SCI.....</i>                                          | 254        |
| <i>Neurotrophic factor changes in SCI .....</i>                                  | 255        |
| <b>Management of SCI .....</b>                                                   | <b>256</b> |
| <b>Pharmacological neuroprotective agents for SCI .....</b>                      | <b>257</b> |
| 4-aminopyridine .....                                                            | 257        |
| Antibodies as neurite growth inhibitors in SCI.....                              | 257        |
| Antiepileptotoxic agents .....                                                   | 257        |
| <i>Gacyclidine .....</i>                                                         | 257        |
| <i>GM-1 ganglioside .....</i>                                                    | 258        |
| Bacterial enzyme chondroitinase ABC .....                                        | 258        |
| Docosahexaenoic acid as neuroprotective in SCI.....                              | 258        |
| Erythropoietin as a neuroprotective in SCI .....                                 | 259        |
| Free radical scavengers for neuroprotection in SCI.....                          | 259        |
| GYKI 52466 .....                                                                 | 259        |
| Immunosuppressants as neuroprotectants in SCI.....                               | 259        |
| Interleukin-10 for neuroprotection in SCI.....                                   | 260        |
| Matrix metalloproteinase inhibitors for SCI.....                                 | 260        |
| Methylprednisolone .....                                                         | 260        |
| Minocycline as neuroprotective in SCI.....                                       | 261        |
| Modulation of macrophage responses for neuroprotection after SCI.....            | 261        |
| Neurotrophic factors for neuroprotection after SCI .....                         | 262        |
| <i>Promotion of regeneration of neurons in SCI .....</i>                         | 262        |
| Rho pathway and Rho antagonists in SCI .....                                     | 263        |
| Selenium as a neuroprotective for SCI.....                                       | 263        |
| Sialidase for enhancing recovery after SCI .....                                 | 263        |
| Targeting the inflammatory response for neuroprotection in SCI .....             | 264        |
| Uric acid as neuroprotective in SCI.....                                         | 264        |
| <b>Non-pharmacological approaches to SCI .....</b>                               | <b>264</b> |
| Hyperbaric oxygen therapy .....                                                  | 264        |
| Hypothermia for SCI .....                                                        | 264        |
| <b>Cell therapy for SCI .....</b>                                                | <b>265</b> |
| Autoimmune T cells against CNS myelin-associated peptide .....                   | 265        |
| Fetal neural grafts for SCI .....                                                | 265        |
| Olfactory-ensheathing cells for SCI .....                                        | 265        |
| Oligodendrocyte precursor cells for treatment of SCI.....                        | 266        |
| Schwann cell transplants for SCI.....                                            | 266        |
| Transplantation of glial cells for SCI .....                                     | 266        |
| Stem cells for SCI .....                                                         | 266        |
| <i>Bone marrow stem cells for SCI.....</i>                                       | 266        |
| <i>Embryonic stem cells for SCI.....</i>                                         | 267        |
| <i>Transplantation of induced pluripotent stem cells in SCI .....</i>            | 267        |
| <i>Transplantation of MSCs for SCI .....</i>                                     | 268        |
| <i>Transplantation of NSCs for SCI.....</i>                                      | 268        |
| <i>Transdifferentiation of stem cells into cholinergic neurons for SCI .....</i> | 269        |
| <b>Gene therapy for SCI .....</b>                                                | <b>269</b> |
| <b>Combined approaches to spinal cord injury .....</b>                           | <b>270</b> |
| <b>Discovery of new targets for neuroprotective therapies in SCI.....</b>        | <b>270</b> |
| <b>Clinical trials in SCI.....</b>                                               | <b>271</b> |
| <b>6. Neuroprotection in Neurodegenerative Disorders.....</b>                    | <b>272</b> |
| <b>Introduction .....</b>                                                        | <b>272</b> |
| <b>Pathomechanism of neurodegeneration .....</b>                                 | <b>272</b> |
| Aging and neurodegeneration.....                                                 | 272        |
| α-synuclein in neurodegeneration and neuroprotection .....                       | 273        |
| Dysregulation of cyclin-dependent kinase 5.....                                  | 273        |
| Exosomes in CNS neurodegeneration and neuroregeneration.....                     | 273        |
| Genomics of neurodegenerative diseases.....                                      | 274        |
| Impairment of neural transport in neurodegenerative disorders .....              | 274        |
| Lack of neurotrophic factors .....                                               | 274        |
| Neuroinflammation in neurodegenerative disorders .....                           | 275        |
| Neurodegeneration associated with protein misfolding .....                       | 275        |
| <i>Modulation of neurodegeneration by molecular chaperones .....</i>             | 275        |
| <i>Intrabodies targeting protein misfolding in neurodegeneration.....</i>        | 276        |
| <i>Targeting proteins aggregation to prevent amyloid formation .....</i>         | 276        |
| <i>Tau and neurodegeneration.....</i>                                            | 276        |

|                                                                                   |            |
|-----------------------------------------------------------------------------------|------------|
| Role of apoptosis in neurodegenerative disorders .....                            | 277        |
| Role of glia in neurodegeneration .....                                           | 277        |
| Role of metals in neurodegeneration .....                                         | 277        |
| Spread of neurodegeneration .....                                                 | 277        |
| TDP-43 proteinopathy and neurodegenerative diseases .....                         | 278        |
| Viral infections and neurodegeneration .....                                      | 278        |
| <i>AIDS and the nervous system</i> .....                                          | 278        |
| <i>Avian influenza as cause of neurodegeneration</i> .....                        | 279        |
| <b>Neurodegenerative disorders with dementia .....</b>                            | <b>280</b> |
| Dementia with Lewy bodies .....                                                   | 280        |
| Frontotemporal dementia .....                                                     | 281        |
| Progressive supranuclear palsy .....                                              | 282        |
| <b>Genetic disorders with neurodegeneration .....</b>                             | <b>282</b> |
| Batten disease .....                                                              | 282        |
| <i>Cell and gene therapies</i> .....                                              | 282        |
| <i>Cerliponase alfa</i> .....                                                     | 283        |
| Familial dysautonomia .....                                                       | 284        |
| Friedrich ataxia .....                                                            | 284        |
| <i>Pathomechanism of FA</i> .....                                                 | 284        |
| <i>Neuroprotection in FA</i> .....                                                | 284        |
| Leigh syndrome .....                                                              | 285        |
| Niemann-Pick type C disease .....                                                 | 285        |
| Spinal and bulbar muscular atrophy .....                                          | 286        |
| <i>Spinal muscular atrophy</i> .....                                              | 286        |
| <b>Creutzfeldt-Jakob disease .....</b>                                            | <b>287</b> |
| Neuroprotection in Creutzfeldt-Jakob disease .....                                | 288        |
| <i>Pharmacological neuroprotectants against CJD</i> .....                         | 288        |
| <i>Innovative approaches to neuroprotection in CJD and future prospects</i> ..... | 289        |
| <b>Approaches to neuroprotection in neurodegenerative disorders .....</b>         | <b>290</b> |
| Glutamate-based therapies for neurodegenerative disorders .....                   | 290        |
| Histone deacetylase inhibitors for neurodegenerative disorders .....              | 291        |
| Iron chelation for neuroprotection .....                                          | 291        |
| Mitochondria permeability transition pore complex and neuroprotection .....       | 291        |
| Modulation of proteostasis in neurodegenerative disorders .....                   | 291        |
| <b>7. Neuroprotection in Parkinson Disease .....</b>                              | <b>294</b> |
| <b>Introduction .....</b>                                                         | <b>294</b> |
| <b>Epidemiology of Parkinson's disease .....</b>                                  | <b>294</b> |
| <b>Pathophysiology of Parkinson's disease .....</b>                               | <b>294</b> |
| Alteration of dopamine homeostasis .....                                          | 295        |
| Apoptosis .....                                                                   | 295        |
| Asynchronous neuronal activity .....                                              | 295        |
| Calcium interaction with $\alpha$ -synuclein .....                                | 296        |
| Disruption of iron homeostasis .....                                              | 296        |
| Excitotoxicity .....                                                              | 296        |
| Genes and PD .....                                                                | 296        |
| Oxidative stress .....                                                            | 298        |
| Role of neurotrophic factors .....                                                | 299        |
| Role of misfolding proteins .....                                                 | 299        |
| Role of $\alpha$ -synuclein in dementia of PD .....                               | 299        |
| Synaptic vesicle glycoprotein 2C disruption in PD .....                           | 300        |
| <b>Neuroprotective strategies for PD based on pathomechanism .....</b>            | <b>300</b> |
| A genetic animal model of PD for testing neuroprotective strategies .....         | 301        |
| Aldehyde dehydrogenase 1 protects nigrostriatal dopaminergic neurons .....        | 302        |
| RNAi screening to identify neuroprotective genes in a PD model .....              | 302        |
| Strategies to stop aggregation of $\alpha$ -synuclein .....                       | 302        |
| <b>Management of Parkinson's disease .....</b>                                    | <b>303</b> |
| Limitation of conventionally administered dopamine therapy .....                  | 304        |
| <b>Neuroprotective therapy in PD .....</b>                                        | <b>304</b> |
| <b>Neuroprotective effect of currently used drugs for PD .....</b>                | <b>305</b> |
| Pramipexole .....                                                                 | 305        |
| Rasagiline mesylate .....                                                         | 306        |
| Ropinirole .....                                                                  | 306        |
| Rivastigmine for treatment of dementia and falls associated with PD .....         | 307        |
| Selegiline .....                                                                  | 307        |
| <b>Non-pharmacological strategies for neuroprotection in PD .....</b>             | <b>308</b> |
| Deep brain stimulation for PD .....                                               | 308        |
| Effect of exercise and environmental enrichment on PD .....                       | 309        |
| Low-calorie diet in PD .....                                                      | 309        |
| <b>Development of neuroprotective therapies for PD .....</b>                      | <b>309</b> |
| 2B3-201 for targeted delivery of methylprednisolone .....                         | 309        |

|                                                                             |            |
|-----------------------------------------------------------------------------|------------|
| 9-methyl- $\beta$ -carboline.....                                           | 310        |
| Adenosine A <sub>2</sub> receptor antagonists .....                         | 310        |
| Antiapoptotic strategies for PD .....                                       | 311        |
| ATP13A2 activation .....                                                    | 311        |
| Augmenting CNS glucocerebrosidase activity.....                             | 311        |
| $\beta$ 2-Adrenoreceptor agonists .....                                     | 311        |
| Calcium channel blockers for PD .....                                       | 312        |
| Cell therapies for PD.....                                                  | 312        |
| <i>Stem cells for PD</i> .....                                              | 312        |
| <i>Activation of endogenous stem cells and neural precursors</i> .....      | 313        |
| Cogane.....                                                                 | 313        |
| Creatine and minocycline.....                                               | 314        |
| Conserved dopamine neurotrophic factor for PD.....                          | 314        |
| Doxycycline as a neuroprotectant in PD.....                                 | 314        |
| Free radical scavengers for neuroprotection in Parkinson's disease.....     | 315        |
| <i>Antioxidants</i> .....                                                   | 315        |
| <i>Diapocynin</i> .....                                                     | 315        |
| <i>Tea extracts as neuroprotectives</i> .....                               | 315        |
| Gene therapy for PD.....                                                    | 316        |
| <i>Implantation of genetically engineered cells</i> .....                   | 317        |
| <i>Gene therapy using GDNF and neurturin</i> .....                          | 317        |
| <i>Glutamic acid decarboxylase gene therapy</i> .....                       | 318        |
| <i>Parkin gene therapy</i> .....                                            | 318        |
| <i>Concluding remarks about gene therapy for PD</i> .....                   | 318        |
| Heat shock protein 70 .....                                                 | 319        |
| Liver X receptor $\beta$ agonists.....                                      | 319        |
| Melatonin as a neuroprotectant in PD .....                                  | 319        |
| Nicotine as a neuroprotective in PD .....                                   | 320        |
| Nilotinib for PD .....                                                      | 320        |
| Neuroprotective effect of leucine-rich repeat kinase-2 inhibitors .....     | 321        |
| Neuroprotective effect of DJ-1 protein .....                                | 321        |
| Neurotrophic factors.....                                                   | 321        |
| <i>Basic fibroblast growth factor for PD</i> .....                          | 321        |
| <i>BDNF for PD</i> .....                                                    | 321        |
| <i>GDNF for PD</i> .....                                                    | 322        |
| <i>MANF for PD</i> .....                                                    | 322        |
| <i>Neurturin for PD</i> .....                                               | 323        |
| <i>Platelet derived growth factor</i> .....                                 | 323        |
| <i>Clinical trials with NTFs</i> .....                                      | 323        |
| Nrf2-mediated neuroprotection in PD.....                                    | 323        |
| Nuclear receptor-related 1:Retinoid X receptor $\alpha$ activation .....    | 324        |
| Omega-3 polyunsaturated fatty acids .....                                   | 324        |
| RAB3B overexpression.....                                                   | 324        |
| RNAi therapy for PD .....                                                   | 325        |
| Safinamide.....                                                             | 325        |
| Sirtuin 2 inhibitors for neuroprotection in PD .....                        | 325        |
| Squalamine and PD .....                                                     | 326        |
| Statins and PD.....                                                         | 326        |
| Targeting Bax.....                                                          | 326        |
| Vitamin D for neuroprotection in PD .....                                   | 327        |
| Vaccine for PD.....                                                         | 327        |
| <b>Clinical trials of neuroprotection in Parkinson's disease .....</b>      | <b>328</b> |
| <b>Evaluation of neuroprotective therapies for PD .....</b>                 | <b>329</b> |
| <b>Current status and future challenges for neuroprotection in PD .....</b> | <b>330</b> |
| <b>8. Neuroprotection in Alzheimer Disease.....</b>                         | <b>332</b> |
| <b>Introduction .....</b>                                                   | <b>332</b> |
| <b>Pathomechanism of Alzheimer's disease .....</b>                          | <b>332</b> |
| Role of glutamate transport dysfunction in AD .....                         | 333        |
| Role of neurotrophic factors in the pathomechanism of AD .....              | 333        |
| <b>Management of Alzheimer's disease .....</b>                              | <b>333</b> |
| <b>Neuroprotection in Alzheimer's disease.....</b>                          | <b>334</b> |
| <b>Inhibition of A<math>\beta</math> formation and aggregation.....</b>     | <b>335</b> |
| AN-1792 .....                                                               | 335        |
| Clioquinol.....                                                             | 336        |
| Colostrinin .....                                                           | 336        |
| FKBP52 for neuroprotection from Cu toxicity in AD.....                      | 337        |
| Monoclonal antibody m266.....                                               | 337        |
| Phenserine .....                                                            | 337        |
| Secretase inhibitors.....                                                   | 338        |
| <b>Inhibition of neuroinflammation .....</b>                                | <b>338</b> |

|                                                                         |            |
|-------------------------------------------------------------------------|------------|
| Etanercept .....                                                        | 338        |
| <b>Neurotrophic factors for neuroprotection in AD .....</b>             | <b>339</b> |
| AL-108 .....                                                            | 339        |
| NGF gene therapy .....                                                  | 339        |
| Small molecule compounds binding to neurotrophin receptor p75NTR.....   | 340        |
| Targeting plasminogen activator inhibitor type-1 gene.....              | 341        |
| <b>Estrogen and AD .....</b>                                            | <b>341</b> |
| <b>Antioxidants .....</b>                                               | <b>342</b> |
| NSAIDS .....                                                            | 342        |
| <b>Melatonin for AD .....</b>                                           | <b>342</b> |
| <b>Memantine.....</b>                                                   | <b>342</b> |
| <b>Dimebon .....</b>                                                    | <b>343</b> |
| <b>Cerebrolysin .....</b>                                               | <b>344</b> |
| <b>Curcumin as a neuroprotectant in Alzheimer disease .....</b>         | <b>344</b> |
| <b>Ginko biloba.....</b>                                                | <b>344</b> |
| <b>Tetrahydrocannabinol for neuroprotection in AD .....</b>             | <b>345</b> |
| <b>Ladostigil tartrate.....</b>                                         | <b>346</b> |
| <b>Phosphodiesterase inhibitors as neuroprotectives.....</b>            | <b>346</b> |
| <b>PPAR-<math>\gamma</math> agonists .....</b>                          | <b>346</b> |
| <b>Role of statins in reducing the risk of AD .....</b>                 | <b>346</b> |
| <b>Combined therapeutic approaches to AD .....</b>                      | <b>347</b> |
| <b>Clinical trials in AD.....</b>                                       | <b>347</b> |
| <b>Future prospects of neuroprotection in AD .....</b>                  | <b>358</b> |
| <b>Mild cognitive impairment .....</b>                                  | <b>359</b> |
| Relation of MCI to AD .....                                             | 359        |
| Neuroprotection in MCI .....                                            | 360        |
| <i>Pharmacological approaches for MCI .....</i>                         | <i>360</i> |
| <i>Non-pharmacological approaches to MCI.....</i>                       | <i>360</i> |
| <br>                                                                    |            |
| <b>9. Neuroprotection in Huntington Disease .....</b>                   | <b>362</b> |
| <b>Introduction .....</b>                                               | <b>362</b> |
| <b>Pathophysiology of HD.....</b>                                       | <b>362</b> |
| <b>Management of Huntington's disease .....</b>                         | <b>364</b> |
| <b>Neuroprotection in Huntington's disease .....</b>                    | <b>364</b> |
| Antipsychotic D <sub>2</sub> and 5-HT <sub>1A</sub> antagonists .....   | 365        |
| Caspase inhibitors.....                                                 | 365        |
| Clioquinol for HD.....                                                  | 366        |
| Creatine for stabilizing bioenergetic defects.....                      | 366        |
| Cysteine and neuroprotection in HD .....                                | 366        |
| <i>Cysteine metabolism reprogramming for neuroprotection in HD.....</i> | <i>366</i> |
| <i>Cysteamine .....</i>                                                 | <i>366</i> |
| Drugs that block inappropriate calcium release from neurons .....       | 367        |
| Enhancing protease activity for clearance of mHtt.....                  | 367        |
| Eicosapentaenoic acid.....                                              | 367        |
| Free radical scavengers .....                                           | 368        |
| Histone deacetylase inhibitors .....                                    | 368        |
| Metal-protein attenuating compounds.....                                | 368        |
| Phosphodiesterase inhibitors .....                                      | 369        |
| Polyglutamine aggregation inhibitors .....                              | 369        |
| Pridopidine.....                                                        | 369        |
| RRAS signaling pathway inhibition.....                                  | 370        |
| Simvastatin as a neuroprotective in HD .....                            | 370        |
| Single chain Fv antibodies .....                                        | 370        |
| SIRT1 activators for neuroprotection in HD .....                        | 371        |
| SIRT2 inhibitors for neuroprotection in HD .....                        | 371        |
| Synaptic activation of NMDA receptors.....                              | 371        |
| Targeting mutant huntingtin protein.....                                | 372        |
| Tetrabenazine .....                                                     | 373        |
| Combinatorial therapy and targeting multiple pathways in HD .....       | 373        |
| Cell therapy for HD .....                                               | 374        |
| <i>Cell transplants for HD.....</i>                                     | <i>374</i> |
| <i>Stem cell-based therapy for HD .....</i>                             | <i>374</i> |
| Neurotrophic factors and gene therapy .....                             | 375        |
| RNAi and antisense therapies for Huntington's disease .....             | 376        |
| <br>                                                                    |            |
| <b>10. Neuroprotection in Amyotrophic Lateral Sclerosis .....</b>       | <b>378</b> |
| <b>Introduction .....</b>                                               | <b>378</b> |
| <b>Pathophysiology of ALS .....</b>                                     | <b>378</b> |
| <b>Neuroprotective therapies for ALS.....</b>                           | <b>383</b> |
| Activated protein C .....                                               | 384        |
| AEOL 10150 .....                                                        | 384        |



|                                                                   |            |
|-------------------------------------------------------------------|------------|
| AIMSPRO .....                                                     | 385        |
| Anakinra .....                                                    | 385        |
| Antisense therapy .....                                           | 385        |
| Arimoclomol for ALS .....                                         | 386        |
| Ceftriaxone for ALS .....                                         | 386        |
| Coenzyme Q10 for ALS .....                                        | 386        |
| COX-2 inhibitors for ALS .....                                    | 387        |
| Creatine for ALS .....                                            | 387        |
| Dexpramipexole.....                                               | 387        |
| Diallyl trisulfide.....                                           | 388        |
| Edaravone for ALS .....                                           | 388        |
| Erythropoietin for ALS .....                                      | 388        |
| Gene therapy for ALS .....                                        | 388        |
| Glatiramer acetate .....                                          | 389        |
| GM602 .....                                                       | 389        |
| Insulin-like growth factor .....                                  | 389        |
| Ketogenic diet for neuroprotection in ALS.....                    | 390        |
| Lenalidomide.....                                                 | 390        |
| Lithium for neuroprotection in ALS .....                          | 391        |
| Masitinib .....                                                   | 391        |
| Melatonin for ALS.....                                            | 391        |
| Methylcobalamin.....                                              | 392        |
| Minocycline for ALS .....                                         | 392        |
| Olesoxime as neuroprotective for ALS.....                         | 392        |
| ONO-2506 for ALS .....                                            | 392        |
| Riluzole .....                                                    | 393        |
| RNAi-based therapy for ALS .....                                  | 393        |
| Sodium phenylbutyrate.....                                        | 393        |
| Stem cell therapy.....                                            | 394        |
| <i>Clinical applications</i> .....                                | 394        |
| <i>Stem cell-based drug discovery for ALS</i> .....               | 394        |
| <i>Suppressors of mTDP-43 toxicity</i> .....                      | 395        |
| Talampanel .....                                                  | 395        |
| Tamoxifen.....                                                    | 396        |
| Vaccination for ALS caused by SOD1 mutations .....                | 396        |
| Vascular endothelial growth factor for ALS .....                  | 396        |
| Vitamin E for ALS.....                                            | 397        |
| <b>Clinical trials of neuroprotective therapies for ALS .....</b> | <b>397</b> |
| <b>Concluding remarks and future prospects.....</b>               | <b>400</b> |
| Use of CRISPR/Cas9 technology to find new targets in ALS .....    | 401        |
| Concluding remarks on neuroprotection in ALS .....                | 401        |

## **11. Neuroprotection in Miscellaneous Neurological Disorders ..... 402**

|                                                                                 |            |
|---------------------------------------------------------------------------------|------------|
| <b>Introduction .....</b>                                                       | <b>402</b> |
| <b>Neuroprotection in synaptopathies.....</b>                                   | <b>402</b> |
| Neuroprotection in ASD .....                                                    | 403        |
| Neuroprotection in fragile X syndrome.....                                      | 403        |
| <b>Neuroprotection in dementia .....</b>                                        | <b>403</b> |
| Age-related dementia .....                                                      | 403        |
| <i>Aging brain and oxidative stress</i> .....                                   | 404        |
| <i>Enhancing endogenous neurotrophic support of the aging brain</i> .....       | 404        |
| <i>Hsp70 and age-related neurodegeneration</i> .....                            | 405        |
| <i>Pharmacological approaches for treatment of age-related dementia</i> .....   | 405        |
| <i>Physical exercise to prevent decline of mental function with aging</i> ..... | 406        |
| Vascular dementia .....                                                         | 406        |
| <i>Prediction of dementia in persons with vascular risk factors</i> .....       | 407        |
| <i>Management of subcortical vascular dementia</i> .....                        | 407        |
| Dementia with Lewy bodies .....                                                 | 408        |
| Neuroprotection in AIDS dementia .....                                          | 408        |
| <b>Multiple system atrophy .....</b>                                            | <b>409</b> |
| <b>Epilepsy .....</b>                                                           | <b>410</b> |
| Mechanisms of neuronal damage in epilepsy .....                                 | 410        |
| Strategies for neuroprotection in epilepsy .....                                | 411        |
| AEDs and neuroprotection.....                                                   | 411        |
| Cell therapy for neuroprotection in epilepsy .....                              | 412        |
| <i>Cell therapy of posttraumatic epilepsy</i> .....                             | 413        |
| <i>Cell therapy for temporal lobe epilepsy</i> .....                            | 413        |
| <i>Cell therapy for pharmacoresistant epilepsies</i> .....                      | 414        |
| Drugs targeting mossy cells in drug-resistant epilepsy.....                     | 414        |
| Gene therapy for neuroprotection in epilepsy .....                              | 414        |
| Hyaluronan-based preservation of brain ECS volume.....                          | 415        |

|                                                                                                   |            |
|---------------------------------------------------------------------------------------------------|------------|
| Hypothermia for neuroprotection in status epilepticus.....                                        | 415        |
| Ketogenic diet for prevention of seizures.....                                                    | 416        |
| miR-211 as an attenuator of cholinergic-mediated seizures.....                                    | 416        |
| <b>Multiple sclerosis.....</b>                                                                    | <b>416</b> |
| Introduction.....                                                                                 | 416        |
| Epidemiology of multiple sclerosis.....                                                           | 416        |
| Pathophysiology.....                                                                              | 417        |
| Current management of multiple sclerosis.....                                                     | 417        |
| Specific therapies for MS based on pathomechanism.....                                            | 418        |
| Neuroprotection in multiple sclerosis.....                                                        | 419        |
| Clinical trials of neuroprotective therapies for MS.....                                          | 420        |
| Neuroprotection by control of progressive forms of multiple sclerosis.....                        | 421        |
| Neuroprotection by controlling autoimmune inflammation in the brain.....                          | 421        |
| Neuroprotection by sealing the BBB with imatinib.....                                             | 422        |
| TRPM4 cation channel blockers.....                                                                | 422        |
| Remyelination for neuroprotection in multiple sclerosis.....                                      | 423        |
| Agents for neuroprotection in multiple sclerosis.....                                             | 423        |
| <i>Angiotensin-II inhibitors</i> .....                                                            | 423        |
| <i>Antigliutamate agents</i> .....                                                                | 423        |
| <i>Antioxidants for neuroprotection in MS</i> .....                                               | 424        |
| <i>Antisense and RNAi approaches to MS</i> .....                                                  | 424        |
| <i>B cell depletion therapy</i> .....                                                             | 424        |
| <i>Cell therapy for multiple sclerosis</i> .....                                                  | 425        |
| <i>Cannabinoids for neuroprotection in MS</i> .....                                               | 427        |
| <i>Cladribine</i> .....                                                                           | 428        |
| <i>Curcumin as a neuroprotectant in multiple sclerosis</i> .....                                  | 428        |
| <i>Cytokine-directed therapies in MS</i> .....                                                    | 428        |
| <i>Dalfampridine in MS</i> .....                                                                  | 429        |
| <i>Dimethyl fumarate</i> .....                                                                    | 429        |
| <i>DNA vaccine for MS</i> .....                                                                   | 429        |
| <i>Erythropoietin as a neuroprotective in MS</i> .....                                            | 430        |
| <i>Fingolimod</i> .....                                                                           | 430        |
| <i>Fusokine composed of GM-CSF and IL-15 for immune suppression</i> .....                         | 431        |
| <i>Gene therapy for MS</i> .....                                                                  | 431        |
| <i>Ibudilast for MS</i> .....                                                                     | 431        |
| <i>Iron chelators</i> .....                                                                       | 432        |
| <i>IVIG for MS</i> .....                                                                          | 432        |
| <i>Kinase inhibitors</i> .....                                                                    | 432        |
| <i>Laquinimod</i> .....                                                                           | 432        |
| <i>Melatonin for MS</i> .....                                                                     | 433        |
| <i>Minocycline for MS</i> .....                                                                   | 433        |
| <i>Monoclonal antibodies for MS</i> .....                                                         | 433        |
| <i>Natalizumab</i> .....                                                                          | 434        |
| <i>Natural human antibodies for repair of myelin</i> .....                                        | 435        |
| <i>Neurotrophic factors for multiple sclerosis</i> .....                                          | 435        |
| <i>Nimodipine</i> .....                                                                           | 436        |
| <i>Oral immunomodulatory agents for MS</i> .....                                                  | 436        |
| <i>Protein kinase C<math>\beta</math> as a therapeutic target for stabilizing BBB in MS</i> ..... | 437        |
| <i>Recombinant T-cell ligands</i> .....                                                           | 437        |
| <i>Statins for MS</i> .....                                                                       | 437        |
| <i>Teriflunomide</i> .....                                                                        | 438        |
| <i>Tolerance-directed immunotherapy for MS</i> .....                                              | 438        |
| Concluding remarks and future prospects for neuroprotection in MS.....                            | 438        |
| <b>Neuroprotection in anti-NMDA receptor encephalitis.....</b>                                    | <b>439</b> |
| <b>Neuroprotection in transverse myelitis.....</b>                                                | <b>439</b> |
| <b>Neuroprotection in decompression sickness.....</b>                                             | <b>440</b> |
| <b>Neuroprotection in victims of drowning.....</b>                                                | <b>441</b> |
| <b>Neuroprotection in CSF circulatory disorders.....</b>                                          | <b>441</b> |
| Neuroprotection in hydrocephalus.....                                                             | 441        |
| Neuroprotection in normal pressure hydrocephalus.....                                             | 442        |
| <b>Neuroprotection in infections of the CNS.....</b>                                              | <b>442</b> |
| Neuroprotection in bacterial meningitis.....                                                      | 443        |
| <i>Mechanism of neural injury in bacterial meningitis</i> .....                                   | 443        |
| <i>Strategies for neuroprotection</i> .....                                                       | 443        |
| Neuroprotection in cryptococcal meningitis.....                                                   | 444        |
| Neuroprotective approach to rabies.....                                                           | 444        |
| Neuroprotection in cerebral malaria.....                                                          | 445        |
| <b>Neuroprotection in complications of systemic disorders.....</b>                                | <b>445</b> |
| Neurological complications of cardiovascular disorders.....                                       | 445        |
| <i>Neuroprotection after myocardial infarction</i> .....                                          | 445        |
| <i>Neuroprotection in hypertensive encephalopathy</i> .....                                       | 445        |

|                                                                                      |            |
|--------------------------------------------------------------------------------------|------------|
| <i>Management of hypertension to prevent dementia</i> .....                          | 446        |
| Neuroprotection in complications of diabetes .....                                   | 446        |
| <i>Neuroprotection in hypoglycemic coma</i> .....                                    | 446        |
| <i>Neuroprotection in diabetic ketoacidosis</i> .....                                | 447        |
| <i>Neuroprotection in diabetic retinopathy</i> .....                                 | 448        |
| Neurological complications of liver disorders .....                                  | 448        |
| <i>Hepatic encephalopathy</i> .....                                                  | 448        |
| <i>Bilirubin encephalopathy</i> .....                                                | 449        |
| Neuroprotection in neurological complications of renal disease. ....                 | 450        |
| Neuroprotection in fever .....                                                       | 451        |
| <i>Pharmacologic approaches for fever</i> .....                                      | 453        |
| <i>Cooling the brain for neuroprotection</i> .....                                   | 453        |
| <b>Neuroprotection in toxic encephalopathies</b> .....                               | <b>453</b> |
| Encephalopathy due to organophosphorus poisoning .....                               | 453        |
| Neuroprotection against chemotherapy-induced brain damage .....                      | 454        |
| Neuroprotection against alcohol .....                                                | 454        |
| <i>Alcoholic neurologic disorders</i> .....                                          | 454        |
| <i>Fetal alcohol syndrome</i> .....                                                  | 455        |
| <i>Pathogenesis of alcohol-induced damage to the nervous system</i> .....            | 455        |
| <i>Neuroprotection against neurotoxicity of alcohol</i> .....                        | 455        |
| <b>Neuroprotection against exposure to therapeutic radiation</b> .....               | <b>456</b> |
| Neuroprotection against radiation encephalopathy .....                               | 456        |
| Role of SOD in protection against radiation-induced hippocampal dysfunction .....    | 456        |
| Catalase reduces mitochondrial ROS for neuroprotection from proton irradiation ..... | 457        |
| <b>Neuroprotection in hypoxia-ischemia</b> .....                                     | <b>457</b> |
| <b>Neuroprotection of the fetus and the neonate</b> .....                            | <b>457</b> |
| Neuroprotection in preterm babies .....                                              | 458        |
| Neuroprotection in neonatal hypoxic-ischemic brain injury .....                      | 458        |
| <i>Pathomechanism of neonatal hypoxic-ischemic brain injury</i> .....                | 458        |
| <i>Management of neonatal hypoxia-ischemia</i> .....                                 | 459        |
| <i>Approaches to neuroprotection in neonatal hypoxia-ischemia</i> .....              | 459        |
| <i>Hyperbaric oxygen for neonatal hypoxia-ischemia</i> .....                         | 460        |
| <i>Hypothermia for neonatal hypoxia-ischemia</i> .....                               | 460        |
| <i>Melatonin for neonatal hypoxia-ischemia</i> .....                                 | 460        |
| <i>Minocycline for neonatal hypoxia-ischemia</i> .....                               | 460        |
| <i>Nicotinamide mononucleotide adenylyl transferase 1</i> .....                      | 461        |
| <i>Nitric oxide inhalation for neonatal hypoxia-ischemia</i> .....                   | 461        |
| <i>Plasminogen activator inhibitor-1 for neonatal hypoxia-ischemia</i> .....         | 461        |
| <i>Recombinant erythropoietin for neonatal hypoxia-ischemia</i> .....                | 461        |
| <b>Neuroprotection in carbon monoxide poisoning</b> .....                            | <b>462</b> |
| Pathomechanism of CO poisoning as a basis for neuroprotection .....                  | 462        |
| Management of CO poisoning .....                                                     | 463        |
| <b>Neuroprotection after cardiac arrest</b> .....                                    | <b>463</b> |
| <b>Neuroprotection in delayed post-hypoxic leukoencephalopathy</b> .....             | <b>464</b> |
| <b>Neuroprotection in sleep apnea</b> .....                                          | <b>464</b> |
| <b>Neuroprotection in mitochondrial dysfunction</b> .....                            | <b>465</b> |
| Mitochondrial permeability transition .....                                          | 465        |
| Mitochondrial approaches for neuroprotection .....                                   | 466        |
| Methylene blue .....                                                                 | 467        |
| Role of nanolasers in evaluation of mitochondrial neuroprotectants .....             | 467        |
| Neuroprotection in mitochondrial encephalopathies .....                              | 467        |
| <b>Neuroprotection in psychiatric disorders</b> .....                                | <b>468</b> |
| Cognitive impairment in schizophrenia .....                                          | 468        |
| Electroconvulsive therapy and neuroprotection .....                                  | 468        |
| Neuroprotection in schizophrenia .....                                               | 469        |
| Neuroplasticity and neuroprotection in stress-induced psychiatric disorders .....    | 469        |
| <b>Neuroprotection in hearing loss</b> .....                                         | <b>469</b> |
| Causes of hearing loss .....                                                         | 470        |
| Pathomechanism of hearing loss .....                                                 | 470        |
| Prevention and treatment of hearing loss .....                                       | 471        |
| <i>Hyperbaric oxygen for hearing loss</i> .....                                      | 471        |
| <i>Stem cell therapy for hearing loss</i> .....                                      | 471        |
| <i>Auditory hair cell replacement by gene therapy</i> .....                          | 472        |
| <i>Pharmaceutical approaches to hearing loss</i> .....                               | 472        |
| <i>Prevention of drug-induced hearing loss</i> .....                                 | 474        |
| <b>Neuroprotection of peripheral nerves</b> .....                                    | <b>474</b> |
| Neuroprotective agents for peripheral nerves .....                                   | 474        |
| <i>Acetyl-L-carnitine for peripheral nerve injuries</i> .....                        | 474        |
| <i>Atorvastatin for peripheral nerve injuries</i> .....                              | 475        |
| <i>Erythropoietin for neuroprotection in peripheral nerve injuries</i> .....         | 475        |
| Neuroprotection in peripheral nerve injuries .....                                   | 475        |

|                                                                                    |            |
|------------------------------------------------------------------------------------|------------|
| <i>Role of hyperbaric oxygen in peripheral nerve injuries</i> .....                | 475        |
| <i>Role of neurotrophic factors in peripheral nerve injuries</i> .....             | 476        |
| <i>Pharmacological approaches to Schwann cells</i> .....                           | 476        |
| <i>Role of gene therapy in neuroprotection of injured peripheral nerves</i> .....  | 476        |
| <i>Schwann cell transplantation for peripheral nerve injury</i> .....              | 476        |
| <i>Targeting Wallerian degeneration slow protein for neuroprotection</i> .....     | 477        |
| Peripheral neuropathy .....                                                        | 477        |
| <i>Neuroprotection in diabetic neuropathy</i> .....                                | 477        |
| <i>Cell therapy for neuroprotection in diabetic neuropathy</i> .....               | 478        |
| <i>Gene therapy with zinc finger DNA-binding proteins</i> .....                    | 478        |
| <i>Neuroprotection in chemotherapy-induced neuropathy</i> .....                    | 478        |
| Neuroprotection in chronic inflammatory demyelinating polyradiculoneuropathy ..... | 479        |
| Neuroprotection in Charcot-Marie-Tooth disease 1A .....                            | 479        |
| <b>12. Neuroprotection of the Optic nerve and the Retina .....</b>                 | <b>482</b> |
| <b>Introduction .....</b>                                                          | <b>482</b> |
| <b>Optic neuropathy .....</b>                                                      | <b>482</b> |
| Pathophysiology .....                                                              | 482        |
| Neuroprotection in optic neuritis .....                                            | 483        |
| <i>Evaluating efficacy of drugs for optic neuritis</i> .....                       | 484        |
| <i>Flupirtine</i> .....                                                            | 484        |
| <i>Sodium channel blockers</i> .....                                               | 485        |
| <i>Resveratrol</i> .....                                                           | 485        |
| <b>Neuroprotection in optic nerve trauma .....</b>                                 | <b>485</b> |
| Potential regeneration of the optic nerve.....                                     | 486        |
| Subthreshold transpupillary thermotherapy for protection of RGCs .....             | 486        |
| <b>Neuroprotection of optic nerve in glaucoma .....</b>                            | <b>486</b> |
| Aminoguanidine as a neuroprotective in glaucoma .....                              | 488        |
| Antiglutamate agents for neuroprotection of optic nerve .....                      | 488        |
| Betaxolol .....                                                                    | 488        |
| NGF eye drops.....                                                                 | 488        |
| Targeting A $\beta$ in glaucoma treatment.....                                     | 489        |
| TNF- $\alpha$ blockers for neuroprotection in glaucoma .....                       | 489        |
| Concluding remarks about neuroprotection in glaucoma.....                          | 489        |
| <b>Neuroprotection in retinal ischemia.....</b>                                    | <b>489</b> |
| $\beta$ -adrenoceptor antagonists.....                                             | 490        |
| Brimonidine as a neuroprotective in ischemic retinopathy .....                     | 490        |
| Endogenous neuroprotection in the retina .....                                     | 491        |
| Erythropoietin for neuroprotection of retinal ischemia .....                       | 491        |
| Gene therapy for retinal neuroprotection.....                                      | 491        |
| Hyperbaric oxygen for central retinal artery occlusion.....                        | 492        |
| Levodopa for treating non-arteritic anterior ischemic optic neuropathy .....       | 492        |
| Thioredoxin as a neuroprotective agent in retinal ischemia.....                    | 492        |
| <b>Protection against oxygen-induced retinopathy .....</b>                         | <b>492</b> |
| <b>Neuroprotection in macular degeneration .....</b>                               | <b>493</b> |
| Epidemiology.....                                                                  | 493        |
| Pathomechanism of AMD .....                                                        | 493        |
| Current treatment of AMD .....                                                     | 493        |
| Novel neuroprotective strategies against retinal degeneration .....                | 494        |
| Antiangiogenic agents .....                                                        | 495        |
| Humanized MAb against A $\beta$ .....                                              | 496        |
| LXR agonists .....                                                                 | 496        |
| Neurotrophic factors for neuroprotection in AMD .....                              | 497        |
| <i>CNTF for neuroprotection in AMD</i> .....                                       | 497        |
| <i>N-acetylserotonin derivatives</i> .....                                         | 497        |
| Nutritional protection against AMD .....                                           | 497        |
| Progestogenic hormones .....                                                       | 498        |
| Protection of retinal cells from oxidative-stress-induced apoptosis.....           | 498        |
| Sulindac .....                                                                     | 498        |
| Tandospirone .....                                                                 | 498        |
| Cell therapy for macular degeneration .....                                        | 499        |
| <i>Retinal pigment epithelial cells</i> .....                                      | 499        |
| <i>Stem cells</i> .....                                                            | 499        |
| <i>Neural progenitor cells</i> .....                                               | 499        |
| Gene therapy for retinal degeneration .....                                        | 499        |
| RNAi-based treatments for AMD.....                                                 | 500        |
| <b>Neuroprotection in proliferative diabetic retinopathy .....</b>                 | <b>501</b> |
| RNAi-based approaches to diabetic retinopathy.....                                 | 501        |
| <b>Clinical trials for optic nerve and retinal neuroprotection .....</b>           | <b>501</b> |
| <b>13. Neuroprotection during Anesthesia and Surgery .....</b>                     | <b>504</b> |

|                                                                              |            |
|------------------------------------------------------------------------------|------------|
| <b>Introduction .....</b>                                                    | <b>504</b> |
| <b>Anesthetic agents as neuroprotectives .....</b>                           | <b>504</b> |
| Barbiturates .....                                                           | 504        |
| <i>Thiopental</i> .....                                                      | 505        |
| Etomidate .....                                                              | 506        |
| Propofol.....                                                                | 506        |
| Ketamine .....                                                               | 506        |
| Gaseous anesthetics.....                                                     | 507        |
| <i>Isoflurane</i> .....                                                      | 507        |
| <i>Xenon</i> .....                                                           | 507        |
| Local anesthetics .....                                                      | 508        |
| <b>Monitoring of CNS function during anesthesia and surgery .....</b>        | <b>508</b> |
| Monitoring of cerebral function .....                                        | 508        |
| Monitoring of spinal cord function during spinal surgery .....               | 508        |
| <b>Perioperative neuroprotection .....</b>                                   | <b>509</b> |
| <b>Neuroprotection during cardiovascular procedures .....</b>                | <b>510</b> |
| CNS complications of cardiac surgery .....                                   | 510        |
| Neuroprotective strategies during cardiac surgery.....                       | 511        |
| <i>Neuroprotection before anticipated or induced cardiac arrest</i> .....    | 512        |
| <i>Neuroprotection during coronary artery bypass grafting</i> .....          | 512        |
| <i>Preconditioning with hyperbaric oxygen</i> .....                          | 513        |
| <i>Neuroprotection in aortic surgery</i> .....                               | 513        |
| <i>Pharmacologic strategies for neuroprotection in aortic surgery</i> .....  | 514        |
| <b>Cerebral protection during organ transplantation surgery .....</b>        | <b>514</b> |
| <b>Cerebral protection during neurosurgery .....</b>                         | <b>515</b> |
| Cerebral angiography and endovascular surgery .....                          | 515        |
| Cerebral protection during surgery for arteriovenous malformations .....     | 515        |
| Cerebral protection during surgery of intracranial aneurysms .....           | 515        |
| Management of subarachnoid hemorrhage .....                                  | 516        |
| <i>Vasospasm associated with subarachnoid hemorrhage</i> .....               | 516        |
| Cerebral protection during carotid endarterectomy.....                       | 518        |
| Cerebral protection during surgery of brain tumors .....                     | 518        |
| Neuroprotective measures prior to surgery.....                               | 519        |
| <i>HBO preconditioning for neuroprotection during surgery</i> .....          | 519        |
| Neuroprotection following surgery.....                                       | 519        |
| <i>Neuroprotection by cranioplasty after decompressive craniectomy</i> ..... | 520        |

## Tables

|                                                                                                                                                                      |     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Table 1-1: Historical landmarks in the development of neuroprotection .....                                                                                          | 32  |
| Table 1-2: Intrinsic neuroprotective factors.....                                                                                                                    | 37  |
| Table 1-3: Common features of pathophysiology of brain damage in diseases .....                                                                                      | 45  |
| Table 1-4: Place of neuroprotection in management of CNS disorders .....                                                                                             | 47  |
| Table 1-5: Indications for the use of neuroprotection .....                                                                                                          | 47  |
| Table 1-6: Neuroprotective nanoparticles.....                                                                                                                        | 53  |
| Table 2-1: A classification of neuroprotective agents .....                                                                                                          | 56  |
| Table 2-2: The neuroprotective effect of antiepileptic drugs .....                                                                                                   | 66  |
| Table 2-3: Neuroprotective affect of minocycline in animal models.....                                                                                               | 70  |
| Table 2-4: Classification of antioxidants or free radical scavengers with neuroprotective potential.....                                                             | 78  |
| Table 2-5: Role of erythropoietin in the nervous system .....                                                                                                        | 84  |
| Table 2-6: Ionotropic glutamate receptors .....                                                                                                                      | 89  |
| Table 2-7: Classification of metabotropic glutamate receptors (mGluRs).....                                                                                          | 89  |
| Table 2-8: Methods for neuroprotection based on nonpharmacological preconditioning .....                                                                             | 142 |
| Table 3-1: Cerebrovascular diseases that are relevant to neuroprotection.....                                                                                        | 146 |
| Table 3-2: Neuroprotective strategies for stroke .....                                                                                                               | 157 |
| Table 3-3: Selected effective combinations of hypothermia with other neuroprotective strategies<br>for the treatment of ischemic stroke in experimental models ..... | 188 |
| Table 3-4: Neuroprotective gene transfer in models of cerebral ischemia .....                                                                                        | 196 |
| Table 3-5: Neuroprotective gene therapy in animal stroke<br>models .....                                                                                             | 196 |
| Table 3-6: Neuroprotective agents in clinical development for acute cerebrovascular disease .....                                                                    | 198 |
| Table 3-7: Some failed trials for neuroprotective therapy for stroke .....                                                                                           | 202 |
| Table 3-8: Preclinical assessment of neuroprotective agents in acute stroke models.....                                                                              | 211 |
| Table 3-9: Stroke prevention based on control of risk factors .....                                                                                                  | 213 |
| Table 4-1: Classification of closed TBI .....                                                                                                                        | 216 |
| Table 4-2: Current conventional management of traumatic brain injury .....                                                                                           | 225 |
| Table 4-3: Neuroprotective strategies for traumatic brain injury .....                                                                                               | 227 |
| Table 4-4: Intrinsic factors that influence regeneration in the central nervous system .....                                                                         | 246 |
| Table 4-5: A classification of approaches to regeneration of the brain following injury .....                                                                        | 246 |
| Table 4-6: Ongoing or completed clinical trials for neuroprotection in TBI .....                                                                                     | 248 |
| Table 4-7: Discontinued or failed clinical trials for neuroprotection in TBI.....                                                                                    | 249 |
| Table 5-1: Secondary mechanisms in spinal cord injury.....                                                                                                           | 255 |

|                                                                                                   |     |
|---------------------------------------------------------------------------------------------------|-----|
| Table 5-2: Neuroprotective and regenerative approaches for SCI.....                               | 256 |
| Table 5-3: Clinical trials for neuroprotection in SCI .....                                       | 271 |
| Table 6-1: Neurodegenerative disorders with dementia .....                                        | 280 |
| Table 6-2: Drugs in clinical trials for spinal muscular atrophy .....                             | 287 |
| Table 6-3: Approaches to neuroprotection in CJD.....                                              | 288 |
| Table 6-4: Glutamate-based therapies in clinical development for neurodegenerative disorders..... | 290 |
| Table 7-1: Prevalence of Parkinson's disease in major markets 2016-2026 .....                     | 294 |
| Table 7-2: Factors in the etiology of Parkinson's disease.....                                    | 294 |
| Table 7-3: Strategies for the treatment of Parkinson's disease .....                              | 303 |
| Table 7-4: Gene therapy techniques applicable to Parkinson disease .....                          | 316 |
| Table 7-5: Current clinical trials of neuroprotective therapies for Parkinson disease .....       | 328 |
| Table 7-6: Failed clinical trials of neuroprotective therapies for Parkinson disease.....         | 328 |
| Table 7-7: Evaluation of neuroprotective agents for PD .....                                      | 330 |
| Table 8-1: Cholinergic approaches to the treatment of Alzheimer's disease .....                   | 334 |
| Table 8-2: Neuroprotective agents for Alzheimer's disease.....                                    | 334 |
| Table 8-3: Clinical trials for neuroprotection in Alzheimer disease .....                         | 348 |
| Table 8-4: Discontinued, failed or inconclusive clinical trials of Alzheimer disease .....        | 355 |
| Table 8-5: Strategies for discovery of neuroprotective therapies for AD .....                     | 358 |
| Table 9-1: Neuroprotective approaches in HD.....                                                  | 364 |
| Table 10-1: Hypotheses for the pathogenesis of amyotrophic lateral sclerosis .....                | 378 |
| Table 10-2: Genetic diagnostic biomarkers of ALS.....                                             | 381 |
| Table 10-3: Classification of neuroprotective agents for amyotrophic lateral sclerosis.....       | 383 |
| Table 10-4: Clinical trials of neuroprotective therapies for ALS .....                            | 397 |
| Table 10-5: Failed or discontinued trials of neuroprotective therapies for ALS.....               | 398 |
| Table 11-1: Therapeutic approaches to subcortical vascular dementia .....                         | 407 |
| Table 11-2: Measures for neuroprotection against the sequelae of seizures.....                    | 411 |
| Table 11-3: Neuroprotective effect of AEDs in animal models of status epilepticus (SE).....       | 412 |
| Table 11-4: Specific therapies for MS based on postulated pathomechanisms.....                    | 418 |
| Table 11-5: Approved neuroprotective therapies for multiple sclerosis.....                        | 419 |
| Table 11-6: Neuroprotective therapies for multiple sclerosis in clinical trials .....             | 420 |
| Table 11-7: Measures to prevent acute bilirubin encephalopathy .....                              | 450 |
| Table 11-8: Fever associated with neurologic disorders .....                                      | 451 |
| Table 11-9: Approaches to neuroprotection in neonatal hypoxia-ischemia.....                       | 459 |
| Table 11-10: Drugs with neuroprotective effect at mitochondrial level .....                       | 466 |
| Table 11-11: Causes of sensorineural hearing impairment .....                                     | 470 |
| Table 11-12: Strategies for prevention and treatment of sensorineural hearing loss.....           | 471 |
| Table 11-13: Agents for neuroprotection of the peripheral nervous system .....                    | 474 |
| Table 12-1: Causes of optic neuropathy.....                                                       | 482 |
| Table 12-2: Clinical trials of neuroprotective therapies in optic neuritis.....                   | 484 |
| Table 12-3: Neuroprotection of the optic nerve in glaucoma.....                                   | 487 |
| Table 12-4: Strategies for neuroprotection in retinal ischemia .....                              | 489 |
| Table 12-5: Novel neuroprotective strategies against retinal degeneration .....                   | 495 |
| Table 12-6: Clinical trials for retinal neuroprotection .....                                     | 501 |
| Table 13-1: CNS complications associated with cardiac procedures .....                            | 510 |
| Table 13-2: Strategies for protection of the brain during cardiac surgery .....                   | 511 |
| Table 13-3: Medical and surgical methods of cerebral vasospasm management.....                    | 517 |
| Table 13-4: Neuroprotection by prevention of vasospasm.....                                       | 517 |

## Figures

|                                                                                                 |     |
|-------------------------------------------------------------------------------------------------|-----|
| Figure 2-1: Mechanism of neuroprotective effect of sigma-1 receptor agonists .....              | 64  |
| Figure 2-2: NMDA receptor ion channel complex.....                                              | 94  |
| Figure 2-3: Neuroprotective effect of galantamine .....                                         | 117 |
| Figure 3-1: Some steps in the ischemic cascade and site of action of neuroprotectives .....     | 147 |
| Figure 3-2: Relationship between dementia and acute ischemic stroke .....                       | 155 |
| Figure 3-3: Molecules involved in preconditioning for neuroprotection in ischemia.....          | 190 |
| Figure 3-4: A roadmap for neuroprotection .....                                                 | 212 |
| Figure 4-1: Cascade of events following traumatic brain injury .....                            | 218 |
| Figure 4-2: Neurometabolic cascade of mild TBI .....                                            | 219 |
| Figure 4-3: Secondary injury mechanisms after TBI .....                                         | 220 |
| Figure 4-4: Management of raised ICP after TBI .....                                            | 226 |
| Figure 5-1: Pathomechanism of acute spinal cord injury .....                                    | 254 |
| Figure 7-1: Neuroprotective strategies against death of dopamine-containing neurons in PD ..... | 301 |
| Figure 9-1: Role of HTT protein in pathogenesis of HD and points of intervention.....           | 373 |
| Figure 9-2: Antisense therapeutic approaches to HD for lowering huntingtin .....                | 377 |
| Figure 11-1: A schematic overview of synaptopathies.....                                        | 402 |
| Figure 11-2: Common mechanisms of neural damage in cerebral ischemia and seizures.....          | 410 |
| Figure 11-3: Role of neuroprotection in epilepsy and its treatment.....                         | 411 |
| Figure 11-4: Mechanisms of neonatal hypoxia-ischemia and targets for neuroprotection.....       | 459 |