Neurochemical Aspects of Neurotraumatic and Neurodegenerative Diseases
Akhlaq A. Farooqui

Neurochemical Aspects of Neurotraumatic and Neurodegenerative Diseases
This monograph is dedicated to my wife (Tahira), daughter (Soofia), and son (Seraj). Thank you for sharing your lives with me. You all are always in my heart.

Akhlaq A. Farooqui
American population is aging and an increasing number of Americans are afflicted with stroke, spinal cord trauma, traumatic brain injury, and neurodegenerative diseases. These neurological conditions result in the acute as well as gradual and progressive neurodegeneration, which leads to brain dysfunction. Known risk factors for stroke and neurodegenerative diseases include increasing age, genetic polymorphisms, endocrine dysfunction, oxidative stress, neuroinflammation, excitotoxicity, hypertension, infection, and exposure to neurotoxins. In contrast, spinal cord trauma and traumatic brain injury due to motor cycle and car accidents are major causes of death and disability among young people below the mid-thirties in the USA. According to the NINDS approximately 30–40 million Americans are affected by stroke and neurodegenerative diseases each year. The number of people affected with neurological disorders will double every 20 years and will cost the US economy billions of dollars each year in direct health-care costs and lost opportunities. As the baby boomer’s generation ages and the prevalence of neurotraumatic and neurodegenerative diseases increases in the American society, the need to confront and solve the present day health-care crisis becomes more critical than ever before. In fact, there is now an urgent need to expand significantly the national and international efforts to solve the problem of neurotraumatic and neurodegenerative diseases, with special emphasis on prevention. It is estimated that $100 billion/year will be spent on Alzheimer disease alone. In addition to the financial cost, there is an immense emotional burden on patients, their relatives, and caregivers.

Although molecular mechanisms associated with the pathogenesis of neurotraumatic and neurodegenerative diseases remain unknown, oxidative stress, excitotoxicity, inflammation, misfolding, aggregation, and accumulation of proteins, perturbed Ca$^{2+}$ homeostasis, and apoptosis have been implicated as possible causes of neurodegeneration in the above neurological disorders. There have been remarkable developments not only on neurochemical aspects but also on target-based pharmacological therapeutic intervention in neurotraumatic and neurodegenerative diseases in a variety of animal and cell culture models in past 20 years. In the clinical setting, however, these treatments have failed not only due to the heterogeneity (occurrence of neurons, astrocytes, oligodendrocytes, and microglial cells) of brain and spinal cord tissues but also because degenerating neurons and injured
axons within brain and spinal cord are unable to regenerate spontaneously. The therapeutic strategies to re-establish lost neuronal connections in neurotraumatic and neurodegenerative diseases are currently unavailable. The main objective of this monograph is to present readers with cutting edge and comprehensive overview on neurochemical aspects of neurotraumatic (stroke, spinal cord trauma, and traumatic head injury) and neurodegenerative diseases (Alzheimer disease, Parkinson disease, Amyotrophic Lateral Sclerosis, Huntington disease, and prion disease) in a manner that is useful not only to students and teachers but also to researcher scientists and clinicians. This monograph has 10 chapters. Chapter 1 deals with molecular mechanisms associated with neurodegenerative processes in the brain and spinal cord. Chapters 2 and 3 describe molecular mechanism of neurodegeneration in stroke and potential therapeutic approaches for the treatment of ischemic injury in the brain. Chapters 4 and 5 describe cutting-edge information on neurochemical mechanisms of secondary injury in spinal cord trauma and potential therapeutic strategies for spinal cord injury. Chapters 6 and 7 describe molecular mechanism and treatment strategies for traumatic brain injury. Chapters 8 and 9 describe potential molecular mechanisms associated with the pathogenesis of neurodegenerative diseases and progress on pharmacological approaches that can be used for the treatment of neurodegenerative diseases. Finally, Chapter 10 provides readers and researchers with perspective that will be important for the future research work on neurotraumatic and neurodegenerative diseases in brain and spinal cord.

This monograph can be used as supplemental text for a range of neuroscience and neurochemistry courses. Clinicians (neurologists, pathologists, and psychiatrists) will find this book useful for understanding molecular aspects of neurotraumatic and neurodegenerative diseases. These topics fall in a fast-paced research area related to neurodegeneration that provides opportunities for target-based therapeutic intervention. Although many edited books are separately available on molecular mechanism of stroke, spinal cord trauma, traumatic brain injury, and neurodegenerative diseases but, to the best of my knowledge no one has written a monograph on the neurochemical aspects of neurotraumatic and neurodegenerative diseases. The present monograph is the first to provide a comprehensive and comparative description of neurochemical changes in stroke, spinal cord trauma, traumatic brain injury, and various neurodegenerative diseases along with progress on their pharmacological therapy. This monograph not only provides background and refresher information on neurotraumatic and neurodegenerative diseases in the brain and spinal cord to readers not working in this field but also presents a thorough and unique overview on progress that has been made on the neurochemistry and treatment of stroke, spinal cord trauma, traumatic brain injury, and various neurodegenerative diseases for researcher scientists, who are actively working in the field of neurodegeneration.

The choices of topics presented in this monograph are personal. They are based on my interest not only in the neurochemistry of stroke, spinal cord injury, traumatic brain injury, and various neurodegenerative diseases but also in areas where major progress has been made. I have tried to ensure uniformity and mode of presentation as well as a logical progression of subject from one topic to another and
have provided extensive bibliography. For the sake of simplicity and uniformity a large number of figures with chemical structures of drugs used for the treatment of above neurological disorders and line diagrams of colored signal transduction pathways are also included. I hope that my attempt to integrate and consolidate the knowledge on the neurochemistry of neurotraumatic and neurodegenerative diseases will provide the basis of more dramatic advances and developments not only on molecular mechanisms but also on causes and treatment of neurotraumatic and neurodegenerative diseases.

Columbus, Ohio

Akhlaq A. Farooqui
I thank late Professor Lloyd A. Horrocks for introducing and mentoring me to studies on neurodegeneration in acute neural trauma and neurodegenerative diseases. I also express my gratitude to Ann H. Avouris and Melissa Higgs of Springer, New York, for their cooperation, rapid responses to my queries, and professional and able manuscript handling. It has been a pleasure working with them for many years.

Columbus, Ohio

Akhlaq A. Farooqui
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About the Author

Dr. Akhlaq A. Farooqui is a leader in the field of brain phospholipases A₂, bioactive ether lipid metabolism, polyunsaturated fatty acid metabolism, glycerophospholipid-, sphingolipid-, and cholesterol-derived lipid mediators, glutamate-induced neurotoxicity, and neurological disorders. He has discovered the stimulation of plasmalogen-selective phospholipase A₂ (PlsEtn-PLA₂) in brains from patients with Alzheimer disease. Stimulation of PlsEtn-PLA₂ produces plasmalogen deficiency and increases levels of eicosanoids that may be related to the loss of synapses, induction of neuroinflammation, and oxidative stress in brains of patients with Alzheimer disease. Dr. Farooqui has published cutting-edge research on the generation and identification of glycerophospholipid-, sphingolipid-, and cholesterol-derived lipid mediators in kainic acid neurotoxicity by lipidomics. He has previously authored five monographs: Glycerophospholipids in Brain: Phospholipase A₂ in Neurological Disorders (2007); Neurochemical Aspects of Excitotoxicity (2008); Metabolism and Functions of Bioactive Ether Lipids in Brain (2008); Hot Topics in Neural Membrane Lipidology (2009); and Beneficial Effects of Fish Oil on Human Brain (2009). All monographs are published by Springer. Dr. Farooqui has also edited two books: Biogenic Amines: Pharmacological, Neurochemical and Molecular Aspects in the CNS Nova Science Publisher, Hauppauge, NY (2010) and Molecular Aspects of Neurodegeneration and Neuroprotection, Bentham Science Publishers Ltd (2010).
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AD</td>
<td>Alzheimer disease</td>
</tr>
<tr>
<td>ALS</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>ARA</td>
<td>Arachidonic acid</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
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<tr>
<td>Cer</td>
<td>Ceramide</td>
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<tr>
<td>PlsCho</td>
<td>Choline plasmalogen</td>
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<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
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<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
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<tr>
<td>EPOX</td>
<td>Epoxygenase</td>
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<tr>
<td>PlsEtn</td>
<td>Ethanolamine plasmalogen</td>
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<td>HD</td>
<td>Huntington disease</td>
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<tr>
<td>Ins-1,4,5-P$_3$</td>
<td>Inositol-1,4,5-trisphosphate</td>
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<td>LOX</td>
<td>Lipoxygenase</td>
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<td>PD</td>
<td>Parkinson disease</td>
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<tr>
<td>PtdIns4P</td>
<td>Phosphatidylinositol 4-phosphate</td>
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<tr>
<td>PtdH</td>
<td>Phosphatidic acid</td>
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<tr>
<td>PtdCho</td>
<td>Phosphatidylcholine</td>
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<tr>
<td>PtdEtn</td>
<td>Phosphatidylethanolamine</td>
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<tr>
<td>PtdIns</td>
<td>Phosphatidylinositol</td>
</tr>
<tr>
<td>PtdIns(4,5)P$_2$</td>
<td>Phosphatidylinositol 4,5-bisphosphate</td>
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<tr>
<td>PtdSer</td>
<td>Phosphatidylserine</td>
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<tr>
<td>PLA$_2$</td>
<td>Phospholipase A$_2$</td>
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<td>PLC</td>
<td>Phospholipase C</td>
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<td>PLD</td>
<td>Phospholipase D</td>
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<td>PKC</td>
<td>Protein kinase C</td>
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<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<td>Sph</td>
<td>Sphingosine</td>
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1.1 Introduction

Neurodegeneration is a complex, progressive, and multifaceted process that results in neural cell dysfunction and death in brain and spinal cord. Adult brain and spinal cord contain terminally differentiated postmitotic neurons with downregulated cell division controlling mechanisms (silencing of cyclin-dependent kinases) and upregulated anti-apoptotic mechanisms such as neurotrophic factor signaling, antioxidant enzymes, protein chaperones, anti-apoptotic proteins, and ionostatic systems (Nguyen et al., 2002). Under pathological conditions these adaptations are lost, resulting neuronal re-entry into the cell cycle before death (Becker and Bonni, 2005; Krantic et al., 2005). Like other tissues, in brain neural cell death occurs either through (a) apoptosis or (b) necrosis. The necrosis is characterized by the passive cell swelling, intense mitochondrial damage with rapid loss of ATP, alterations in neural membrane permeability, high calcium influx, and disruption of ion homeostasis. This type of cell death leads to membrane lysis and release of intracellular components that induce inflammatory reactions. In contrast, apoptosis is an active process in which caspases (a group of endoproteases with specificity for aspartate residues in protein) are stimulated. Apoptotic cell death is accompanied by cell shrinkage, dynamic membrane blebbing, chromatin condensation, DNA laddering, loss of phospholipids asymmetry, low ATP levels, and mild calcium overload (Sastry and Subba Rao, 2000; Farooqui et al., 2004; Farooqui, 2009). Thus, apoptosis and necrosis are two extremes of a wide spectrum of cell death processes with different mechanistic and morphological features. However, they may share some common mediators and signal transduction processes that are often inseparable. Neurodegeneration occurs at many different levels of neuronal circuitry. It is often accompanied by atrophy of the affected central or peripheral nervous system structures. Neurodegeneration is regulated by many different factors, including, but not limited to, inherited genetic abnormalities, problems in the immune system, and metabolic or mechanical insults to the brain or spinal cord tissues. Neurodegeneration occurs not only in acute neural trauma (ischemia and traumatic injury to brain and spinal cord) but also in neurodegenerative diseases (Alzheimer disease, AD; Parkinson disease, PD; Huntington disease, HD; and
amyotrophic lateral sclerosis, ALS) and neuropsychiatric disorders (schizophrenia and depression) (Farooqui and Horrocks, 2007; Farooqui, 2009). Neurodegeneration in many of above conditions is accompanied with dementia, a multi-faceted cognitive, memory, and functional progressive impairments, which advance with age (Wehr et al., 2006). Thus, dementia is a behavioral syndrome that is closely associated with cerebrovascular dysfunction in neurodegenerative diseases and stroke (Schaller, 2008). It should be noted that vascular dementia literature lacks a clear consensus regarding the neuropsychological and other constituent characteristics associated with various cerebrovascular changes. The rate of neurodegeneration and dementia varies considerably from one disease to another (Fig. 1.1). Dementia is a syndrome due to a chronic or progressive neural disease, with alterations in multiple cortical functions, such as memory, orientation, comprehension, learning, language, and judgment. Demented subjects are unable to perform spoken and written communication, preparing meals, driving, and leisure activities with the same level of independence as they had enjoyed earlier in life (Schaller, 2008). In addition, they also show deterioration in emotions, personal care, and social behavior.

![Fig. 1.1 Rate of neurodegeneration in neurodegenerative conditions. Alzheimer disease (1); head injury (2); other causes (3); multifactorial dementia (4); Parkinson disease (5); and multiple cause dementia (6)](image_url)

Neurodegeneration in acute neural trauma and neurodegenerative diseases is also associated with disturbed glycerophospholipid metabolism in neural membranes, activation of phospholipases A2, and generation of glycerophospholipid degradation products, which include the production of reactive oxygen species (ROS) and lipid hydroperoxides. Both these metabolites induce oxidative stress (Farooqui and Horrocks, 2007; Farooqui, 2009). A major source for vascular and neuronal ROS is a family of non-phagocytic NADPH oxidases, including the prototypic Nox2 homolog-based NADPH oxidase, as well as other NADPH oxidases, such as Nox1 and Nox4 (Sun et al., 2007). Other possible sources include mitochondrial electron transport enzymes, xanthine oxidase, cyclooxygenase, lipoxygenase, and uncoupled nitric oxide synthase. NADPH oxidase-derived ROS plays a physiological
1.1 Introduction

role in the regulation of neural and endothelial function. At present, pathophysi-
ological importance of neural membrane glycerophospholipid breakdown in acute
neural trauma and neurodegenerative diseases is not fully understood. However, it
is proposed that glycerophospholipid degradation in acute neural trauma may be
an earliest event (Farooqui and Horrocks, 2007). In contrast, in neurodegenera-
tive diseases (AD) alterations in neural membrane glycerophospholipids precede
the clinical manifestations of the disease (dementia) (Pettegrew et al., 1995).

Neurodegenerative diseases and neuropsychiatric disorders fall in a large group
of neurological disorders with heterogeneous clinical and pathological expressions
affecting specific subsets of neurons in specific functional anatomic regions of
brain and spinal cord. Although the exact cause and molecular mechanism of
acute neural trauma, neurodegenerative diseases, and neuropsychiatric disorders
are not fully understood, it is becoming increasingly evident that multiple factors
and mechanisms may contribute to the pathogenesis of above neurological disor-
ders (Bossy-Wetzel et al., 2004; Farooqui and Horrocks, 2007; Farooqui, 2009).
For ischemic injury, the most important factor is lack of oxygen and blood flow
resulting from blocked blood vessels (stroke), traumatic injury which is caused by
shear force of trauma (head and spinal cord injuries), and familial form of neu-
rodegenerative diseases which involve genetic mutations. The most important risk
factors for sporadic neurodegenerative diseases are old age, positive family his-
tory, unhealthy lifestyle, endogenous factors, and exposure to toxic environment
(Fig. 1.2) (Farooqui and Horrocks, 2007). In the brain tissue, aging process is asso-
ciated with elevated mutation load in mitochondrial DNA, defects in mitochondrial

![Fig. 1.2] Factor effecting neurodegeneration in neurological disorders
respiration, and increased oxidative damage (Farooqui and Farooqui, 2009). In aging brain, decline in respiratory function not only results in production of less ATP but also causes elevation in the generation of ROS as by-products of aerobic metabolism. Aging also induces alterations in activities of free radical-scavenging enzymes. In addition, the accumulation of mitochondrial DNA mutations accelerates normal aging, promotes oxidative damage to nuclear DNA, and impairs gene transcription. Thus, normal aging process is accompanied by some level of neurodegeneration, which falls below the threshold of a clinical pathology (Graeber et al., 1998; Farooqui and Farooqui, 2009).

Based on epidemiological and molecular biological studies, it is suggested that in vast majority of sporadic neurodegenerative subjects, genetic contribution to the neurodegenerative process is minimal. Instead, toxic environmental factors and unhealthy lifestyle may contribute to the initiation of neurodegenerative processes (BenMoyal-Segal and Soreq, 2006; Farooqui and Farooqui, 2009). This view is based on the observation that some neurodegenerative diseases arise in geographic or temporal clusters. For example, Guam-type amyotrophic lateral sclerosis/parkinsonism dementia (ALS/PDC) is caused by the presence of β-methylaminoalane (BMAA) in *Cycas circinalis*, an indigenous plant commonly ingested as a food or medicine by the Chamorros of Guam (Murck et al., 2004; Ince and Codd, 2005). Intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a severe and irreversible parkinsonian syndrome that is similar, but not identical, to PD in pathology and progression. In addition, exposure to certain insecticides and herbicides, such as paraquat and rotenone, also produces a Parkinson-like syndrome (Brown et al., 2006; Kamel and Hoppin, 2004; Keifer and Firestone, 2007). However, evidence for the involvement of environmental factors in pathogenesis of neurodegenerative diseases is weak and contradicted by several large-scale epidemiological studies. These studies have failed to show any definitive association between environmental factors and occurrence of neurodegenerative diseases such as AD, PD, HD, and ALS (Brown et al., 2006; Kamel and Hoppin, 2004; Keifer and Firestone, 2007).

Protein folding is a normal biological process associated with the conversion of newly synthesized proteins into physiologically functional molecules. This process is regulated by molecular chaperones that facilitate normal folding, prevent inappropriate interaction between non-native polypeptides, and promote the refolding of proteins that have become misfolded as a result of cellular stress (Muchowski and Wacker, 2005). Cell death in neurodegenerative diseases is accompanied by the accumulation of abnormal extracellular and intracellular deposits caused by misfolding and aggregation of some proteins in some neurons in specific area of the brain (Ross and Poirier, 2004; Farooqui and Farooqui, 2009). Accumulating evidence indicates that at least two pathways modulate protein folding: the ubiquitin-proteasome system (UPS) and molecular chaperone pathway. Downregulation of UPS results in misfolding and aggregation of specific proteins that are often trapped in misfolded conformations in neurodegenerative diseases (Bossy-Wetzel et al., 2004; Ross and Poirier, 2004). To handle a buildup of abnormal misfolded proteins, cells employ a complicated machinery of molecular chaperones.
and various proteolytic systems associated with endoplasmic reticulum (Scheper and Hoozemans, 2009). Chaperones promote refolding of misfolded polypeptides, inhibit protein aggregation, and mediate the formation of aggresome, a centrosome-associated body to which small cytoplasmic aggregates are transported (Merlin and Sherman, 2005). The ubiquitin–proteasome proteolytic system is critical for downregulating the levels of soluble abnormal proteins, while autophagy (a lysosomal pathway) plays the major role in clearing of cells from protein aggregates. The accumulation of prone protein aggregates modulates signal transduction pathways that control cell death, including JNK pathway that regulates viability of a cell in various models of PD and HD (Merlin and Sherman, 2005). Most molecular chaperones passively prevent protein aggregation by interacting with misfolding protein intermediates. Some molecular chaperones and chaperone-related proteases, such as those in proteasome, perform their function by hydrolyzing ATP and forcefully converting stable harmful protein aggregates into harmless natively refoldable, or protease-degradable, polypeptides (Hinault et al., 2006). Collective evidence suggests that molecular chaperones and chaperone-related proteases modulate the delicate balance between natively folded functional proteins and aggregation-prone misfolded proteins, which may accumulate during the lifetime leading to neurodegeneration (Hinault et al., 2006). The major chaperone protein, Hsp72, interferes with this signaling pathway and thus promotes neural cell survival. Other molecular chaperones include protein disulfide isomerase and glucose-regulated protein 78. These proteins also provide neuroprotection from aberrant proteins by facilitating proper folding and thus preventing their aggregation. Molecular chaperones are first line of defense against misfolded, aggregation-prone proteins and are among the most potent suppressors of neurodegeneration. In neurodegenerative diseases, consequences of aggregation and deposition of misfolded proteins are impairment of the ubiquitin–proteasome degradation system and suppression of the heat shock response (Merlin and Sherman, 2005). A common feature of neurodegenerative diseases is a long course in period until sufficient protein accumulates, followed by a cascade of symptoms over many years with increasing disability leading to death. Although normal aging is accompanied by the ability of the brain to modify its own structural organization and functioning that result in loss of some cognitive function, neurodegenerative diseases are accompanied by dramatic impairment in ability to modulate structural organization and functioning of the brain tissue causing a progressive loss of complete cognitive function (Farooqui, 2009).

Recent studies also indicate that generation of excessive nitric oxide (NO) and reactive oxygen species (ROS), in part, due to overactivity of the NMDA subtype of glutamate receptor, can mediate protein misfolding in the absence of genetic predisposition. S-Nitrosylation, or covalent reaction of NO with specific protein thiol groups, represents one mechanism contributing to NO-mediated protein misfolding and neurotoxicity (Uehara, 2007; Nakamura and Lipton, 2009). In addition, a functional relationship between inhibitory S-nitrosylation of the redox enzyme protein disulfide isomerase defects in regulation of protein folding within the endoplasmic reticulum and neurodegeneration. Examination of brains from PD and AD patients supports a causal role for the S-nitrosylation of protein disulfide isomerase and
consequent endoplasmic reticulum stress in these prevalent neurodegenerative disorders (Benhar et al., 2006). Furthermore, increase in levels of S-nitrosylation of dynamin-related protein 1 (SNO-Drp1) triggers neurodegeneration in AD (Cho et al., 2009), and the blockade of nitrosylation of Drp1 by cysteine mutation prevents cell death in AD. Nitrosylation modifies function of many proteins by altering the hydrophobicity, hydrogen bonding, and electrostatic properties within the targeted protein. Nitrosylation in general and S-nitrosylation in particular are regarded as important redox signaling mechanisms in the regulation of many neural cell functions. However, deregulation of S-nitrosylation has been linked to neurodegenerative disorders. Although nitrosative stress has long been considered as a major mediator of neurodegeneration, the molecular mechanism of how NO can contribute to neurodegeneration is not fully established. It is recently suggested that nitration and nitrosylation of proteins contribute to the neurodegenerative process by inducing protein aggregation (Benhar et al., 2006; He et al., 2007; Nakamura and Lipton, 2009).

In addition, under pathophysiological conditions, the excessive generation of NO due to the overactivation of NMDA receptor in neurons or by inducible NO synthase from neighboring glia (microglial cells and astrocytes) results in the interaction between NO and superoxide anion, generated by the mitochondria (2% of the O₂ consumed by healthy mitochondria is converted to superoxide) or by other mechanisms, leading to the formation of the powerful oxidant species, peroxynitrite. Furthermore, the activation of NAD⁺-consuming enzyme poly(ADP-ribose) polymerase-1 (PARP-1) is another likely mechanism for NO-mediated energy failure and neurotoxicity. Although under mild oxidative stress the activation of PARP-1 is a repair process for neuronal protection, under high oxidative stress it causes neuronal energy compromise leading to neurodegeneration (Moncada and Bolanos, 2006; Farooqui, 2009). Nitric oxide also binds to cytochrome c oxidase and is able to inhibit cell respiration in a process that is reversible and in competition with oxygen. This action leads to the release of more superoxide anion from the mitochondrial respiratory chain. Collective evidence suggests that brain aging is accompanied by a higher degree of ROS and NO production, and by diminished functions of mitochondria, endoplasmic reticulum, and the proteasome system, which are responsible for the maintenance of the normal protein homeostasis of the cell. In the event of mitochondrial and endoplasmic reticulum dysfunction, unfolded proteins aggregate forming potentially toxic deposits, which tend to be resistant to degradation. As stated above, neural cells possess adaptive mechanisms, molecular chaperone, and the ubiquitin proteasome system to avoid the accumulation of incorrectly folded proteins to fulfill cellular protein quality control functions (Moncada and Bolanos, 2006; Farooqui, 2009).

Thus, the diversity of neurodegenerative diseases can be explained through the combination of the above pathogenic events: one specific and associated with the aggregation of a particular protein in the nervous system and the other non-specific and associated with aging and with the production and harmful actions of ROS and RNS. This interpretation indicates that the development of drugs capable either of inhibiting the production or aggregation of proteins specifically implicated in
neurodegenerative diseases or blocking the generation or action of ROS and RNS in the brain (Christen, 2002) may be useful for the treatment of neurodegenerative diseases.

Accumulating evidences also support the view that endogenous “biometals,” such as copper, iron, zinc, and exogenous metal ion, aluminum, may also be involved in the etiopathogenesis of a variety of neurodegenerative diseases. Among above metal ions, iron plays a role in oxygen transportation, myelin synthesis, neurotransmitter production, and transfer of electrons (Campbell et al., 2001; Ong and Farooqui, 2005; Valko et al., 2005). Although iron is a crucial cofactor in normal brain metabolism, increased levels of brain iron may promote neurotoxicity due to free radical formation, lipid peroxidation, and ultimately, cellular death. Advanced neuroimaging studies indicate that elevated levels of iron have been observed in patients with neurological diseases, including AD, PD, and stroke. It is also proposed that alterations in the homeostasis of above metal ions may not only contribute to misfolding of accumulating proteins but also promote initiation of plaque aggregation (Zatta et al., 2009).

Neuropsychiatric disorders include both neurodevelopmental disorders and behavioral or psychological difficulties associated with some neurological disorders. An important characteristic of neuropsychiatric disorders is the impairment of cognitive processing. This includes not only ability to learn and store the memory but also to retrieve stored memory for further use and to apply the stored memory to efficiently solve problems (Gallagher, 2004). The impairment of cognitive process may be caused by overexpression or underexpression of certain genes or other unknown factors that result in behavioral symptoms, such as thoughts or actions, delusions, and hallucinations, which are the hallmarks of many neuropsychiatric disorders including schizophrenia, depression, and bipolar disorders. Metabolic defects of the brain, involving myelin sheath (multiple sclerosis) and brain infections (meningitis), do not fall under neurodegenerative disorders.

1.2 Neurodegeneration in Ischemic Injury

Normal functioning of brain needs an uninterrupted supply of both glucose and oxygen. Glucose and oxygen are needed by brain for the synthesis of ATP, which is required not only for maintaining the appropriate ionic gradients across neural membranes (low intracellular Na⁺, high K⁺, and very low cytosolic Ca²⁺) but also for creating optimal cellular redox potentials (Farooqui and Horrocks, 2007). Stroke is a metabolic insult induced by severe reduction or blockade in cerebral blood flow. This blockade not only causes deficiency of oxygen and reduction in glucose metabolism but also results in ATP depletion and accumulation of toxic products. Reduction in ATP is accompanied by impairment in ion homeostasis, glutamate release, and ROS and RNS generation, resulting in neuronal injury and cell death (Farooqui et al., 1994). Within minutes of ischemic insult, proinflammatory genes are upregulated, and adhesion molecules are expressed on the vascular endothelium.
This is accompanied by the migration of neutrophils from the blood into the brain parenchyma within hours after reperfusion (Emerich et al., 2002), followed by the entry of macrophages and monocytes within a few days. Activated microglial cells contribute to vast majority of macrophages in the infarct area before macrophage infiltration from the blood (Schilling et al., 2003). Animal studies indicate that microglial activation also extends beyond the core and can contribute to peri-infarct neuronal death (Mabuchi et al., 2000; Block and Hong, 2005). Microglial activation is accompanied by inflammation, a neuroprotective process (Danton and Dietrich, 2003) associated with promotion of plasticity, modulation of neurotrophic factors, and removal of dead cells (Lalancette-Hebert et al., 2007; Farooqui, 2010).

Few studies have been performed on human stroke due to the inability to collect biopsy and postmortem tissues at time points after the onset of stroke where neuronal death occurs. Information on stroke has been obtained from global or focal animal models of ischemic injury in rodents. In both cases, blood flow disruptions limit the delivery of oxygen and glucose to neurons, causing symptoms and neurochemical changes similar to human stroke. Following stroke, the released glutamate accumulates in the extracellular space and mediates prolonged stimulation of glutamate receptors and a sustained increase in intracellular calcium concentration not only through NMDA receptor channels but also through calcium channels and glutamate transporters operating in the reverse mode. These processes also contribute to the cerebral edema, which is the primary cause of patient mortality after stroke (Farooqui et al., 2008). Neurons are particularly vulnerable to ROS- and RNS-mediated damage not only because of alterations in mitochondrial membrane potential and generation of ROS and RNS but also due to inactivation of glutamine synthetase (Atlante et al., 2000). It decreases glutamate uptake by glial cells and increases glutamate availability at the synapse, producing excitotoxicity (Farooqui et al., 2008). Morphologically glutamate-mediated neurodegeneration (excitotoxicity) is characterized by somatodendritic swelling, chromatin condensation into irregular clumps, and organelle damage. In addition, glutamate also produces neural cell demise by a transporter-related mechanism involving the inhibition of cystine uptake, which decreases glutathione in neural cells and makes them vulnerable to toxic-free radicals (Matute et al., 2006). Major proportions of free radicals originate from glutamate-mediated enhancement of calcium influx, stimulation of phospholipase A2, and oxidation of released arachidonic acid through arachidonic acid cascade, activation of NADPH oxidase, and mitochondrial dysfunction. This increase in intracellular Ca\textsuperscript{2+} also mediates the uncoupling of mitochondrial electron transport and stimulates Ca\textsuperscript{2+}-dependent enzymes including calpains, nitric oxide synthase, protein phosphatases, and various protein kinases (Farooqui et al., 2008). Neurons undergoing severe ischemic injury die rapidly (minutes–hours) by necrotic cell death at the core of injury site, whereas neurons in penumbral region display delayed vulnerability and die through apoptosis (Farooqui et al., 2004, 2008). Which neurons degenerate in ischemic injury depends on which blood vessel is blocked, but often neurons in the cerebral cortex, hippocampus, and striatum are affected. The extent of stroke injury varies according to the age of animals. Thus, 10- and 21-day-old rats develop greater damage from stroke-mediated insult than
1.3 Neurodegeneration in Traumatic Brain Injury and Spinal Cord Trauma

Few studies have been performed on human brain and spinal cord tissues due to the inability to collect biopsy or postmortem tissue at time points after the onset of traumatic injury. Information on traumatic brain and spinal cord injury has been obtained from global or focal animal models in rodents. Traumatic injury to brain and spinal cord is defined by two broad components: a primary component, attributable to the mechanical insult itself, and a secondary component that consists of a series of systemic and local neurochemical changes that occur in the brain and spinal cord after the initial traumatic insult (Klussmann and Martin-Villalba, 2005). The primary injury causes a rapid deformation of brain and spinal cord tissues, leading to the rupture of neural cell membranes and the release of intracellular contents. In contrast, secondary injury to brain and spinal cord includes glial cell reactions involving both activated microglia and astroglia and demyelination involving oligodendroglia (Beattie et al., 2000). Neurochemically, secondary injury is characterized by the release of glutamate from intracellular stores (Panter et al., 1990; Sundstrom and Mo, 2002) and overstimulation of glutamate receptors (excitotoxicity) resulting in a large Ca\(^{2+}\) influx into neurons (Katayama et al., 1990), which not only uncouples of the mitochondrial electron transport but also stimulates Ca\(^{2+}\)-dependent phospholipases A\(_2\) (PLA\(_2\)), phospholipase C (PLC), calpains, nitric oxide synthase, protein phosphatases, matrix metalloproteinases, and various protein kinases (Bazan et al., 1995; Ray et al., 2003; Ellis et al., 2004; Arundine and Tymianski, 2004; Xu et al., 2006). The stimulation of these enzymes not only generates a variety of lipid mediators (Table 1.1) but also rapidly decreases in ATP level, changes ion homeostasis, and alters cellular redox, resulting in the neurodegeneration in the traumatic brain injury and spinal cord trauma. Following brain and spinal cord injury, necrotic cell death normally occurs at the core of injury site whereas apoptotic cell death occurs several hours or days after injury in the surrounding area. Accumulating evidence suggests that excitotoxicity and oxidative stress are major components of brain injury and spinal cord trauma (Farooqui et al., 2004).

1.4 Neurodegeneration in Neurodegenerative Diseases

In general, neurodegeneration in neurodegenerative diseases is accompanied by site-specific premature and slow death of certain neuronal populations in central and peripheral nervous systems (Graeber and Moran, 2002). For example in AD,
Table 1.1 Neurochemical events that are common to acute neural trauma, neurodegenerative diseases, and neuropsychiatric disorders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acute neural trauma</th>
<th>Neurodegenerative diseases</th>
<th>Neuropsychiatric diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate levels</td>
<td>Increased</td>
<td>Alterations in glutamate receptors</td>
<td>Altered</td>
</tr>
<tr>
<td>Calcium</td>
<td>Increased</td>
<td>Altered</td>
<td>Altered</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Neuroinflammation</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Accumulation of aggregated proteins</td>
<td>None</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4-Hydroxynonenal levels</td>
<td>Increased</td>
<td>Increased</td>
<td>–</td>
</tr>
<tr>
<td>Isoprostanes</td>
<td>Increased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Apoptotic cell death</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood–brain barrier permeability</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

Summarized from Farooqui and Horrocks (1994, 2007), Farooqui et al. (2007), McIntosh et al. (1998), Beattie et al. (2000), Block and Hong (2005), and Farooqui (2009).

Neurodegeneration mainly occurs in the nucleus basalis and hippocampal area, whereas in PD, dopaminergic neurons in the substantia nigra undergo neurodegeneration. In HD, neurodegeneration occurs in striatal medium spiny neurons and motor neurons located in the anterior part of spinal cord degenerate in ALS and spinal muscular atrophy (SMA). In Friedreich ataxia (FA), motor neurons found in the posterior part of the spinal cord undergo neurodegeneration (Table 1.2). Some neurodegenerative diseases produce neurodegeneration in cerebellum and cortical atrophy lesions are confined to the Purkinje cells and the inferior olive cells, while in pontocerebellar atrophy neurodegeneration occurs in several cerebellar structures. Despite the important differences in neurochemistry and clinical manifestation, neurodegenerative diseases share some common characteristics such as their commencement late in life, the extensive neuronal death, and loss of synapses, and the presence of cerebral deposits of misfolded protein aggregates (Soto, 2003; Ross and Poirier, 2004). These deposits are a typical disease signature, and although the main protein component of deposits is different in each disease, many accumulated proteins have similar morphological, structural, and staining characteristics. Deposits may be found either outside or inside the dead or dying cells and are generated by abnormal interactions between proteins. Examples of extracellular aggregates are amyloid plaques in AD and prion protein aggregates in bovine spongiform encephalopathy (mad cow disease). Examples of intracellular inclusions are the neurofibrillary tangles in AD and Lewy bodies in PD and the polyglutamine expanded protein aggregates in HD. It should be noted that protein misfolding and deposition in neurodegenerative diseases is the result of an altered balance between protein synthesis, aggregation rate, and clearance. Loss of synapse may also cause protein
Table 1.2 Neurodegeneration sites in neurodegenerative diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Neurodegeneration site</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>Posterior spinal cord</td>
<td>Lodi et al. (2006)</td>
</tr>
</tbody>
</table>

Alzheimer disease (AD); Parkinson disease (PD); Huntington disease (HD); amyotrophic lateral sclerosis (ALS); spinal muscular atrophy (SMA); Friedreich ataxia (FA); cerebellum cortical atrophy (CCA); and pontocerebellar atrophy (PCA).

accumulation, which may be correlated with cognitive impairment in normal aging and different types of dementia in neurodegenerative diseases. Numerous studies indicate the disruption of microtubule-based transport mechanisms as a contributor to synaptic degeneration (Butler et al., 2007). Reported reductions in a microtubule stability marker, acetylated α-tubulin, indicate that disruption transport occurs in AD neurons, and such a reduction is known to be associated with transport failure and synaptic compromise in a hippocampal slice model of protein accumulation (Butler et al., 2007). Collective evidence suggests that degeneration of synapse and disruption of microtubule-based transport may be correlated with cognitive impairment.

Most neurodegenerative diseases are accompanied by elevation in energy demands and reduction in energy production and supply. In neurodegenerative diseases the energy demands of brain are increased due to (a) partial depolarization (Blanchard et al., 2002); (b) impairment in Ca^{2+} homeostasis (Farooqui and Horrocks, 2007); (c) glutamate-mediated increase in neuronal activity (Farooqui et al., 2008); (d) increase in oxidative stress (Farooqui and Horrocks, 2007); and (e) decrease in Na^{+}/K^{+}-ATPases and Ca^{2+}-dependent ATPases (Dickey et al., 2005). At the same time energy production and supply of brain are significantly decreased because of (a) mitochondrial dysfunctions (Kwong et al., 2006; Farooqui et al., 2008); (b) changes in blood flow; and (c) decrease in glucose metabolism/supply (Farooqui and Horrocks, 2007; Farooqui et al., 2008). There is considerable overlapping among above processes and many are coupled by positive feedback mechanisms, as is the energy balance (Kwong et al., 2006). Increased energy deficit promotes increased energy demand and slow neurodegeneration in neurodegenerative diseases.
The neuronal population, which degenerates in neurodegenerative diseases, modulates movements, learning and memory, processing sensory information, and decision-making processes (Rao and Balachandran, 2002). Other risk factors for neurodegenerative diseases include neuroinflammation, autoimmunity, cerebral blood flow, and blood–brain barrier dysfunction (Farooqui et al., 2007; Farooqui and Horrocks, 2007; Farooqui, 2009). For the most part, the nature, time course, and molecular causes of neuronal cell death in neurodegenerative diseases remain unknown, but age-mediated decrease in cellular antioxidant defenses and resultant accumulation of lipid, protein, and DNA damage in central nervous system has been proposed to play an important role in the etiology and pathogenesis of neurodegenerative diseases (Farooqui, 2009) (Fig. 1.3).

In many neurodegenerative diseases, neurodegeneration shortens the life expectancy of patients, but other neurodegenerative diseases are fatal per se. Only those diseases in which neurological structures impair ability to control or execute such vital functions as respiration, heart rate, or blood pressure are deadly (Przedborski et al., 2003). Thus, in ALS, loss of lower motor neurons innervating respiratory muscles leads the patient to succumb to respiratory failure. Alternatively,
in diseases like Friedreich ataxia, the association of neurodegeneration with heart disease can also cause the death of the patient although, in this case, death is not due to any neuronal loss but due to serious cardiac problems, such as congestive heart failure (Przedborski et al., 2003). In other neurodegenerative diseases, death is attributed neither to the disease of the nervous system nor to associated extraneuronal system degeneration, but caused by motor and cognitive impairments that increase the risk of fatal accidental falling, aspiration pneumonia, pressure skin ulcers, malnutrition, and dehydration (Przedborski et al., 2003).

Although some progress has been made on neurochemical alterations and in understanding factors that may trigger neurodegenerative diseases, the precise molecular pathways that lead to neurodegeneration are not fully understood (Farooqui and Horrocks, 2007; Farooqui, 2009). It is proposed that complex interplay between inflammatory mediators, aging, genetic background, oxidative stress, and environmental factors may regulate the progression of chronic neurodegeneration. It should be noted that for every neurodegenerative disease, multiple hypotheses have been proposed to explain the cause of neurodegeneration and neural dysfunction. In many cases, common pathways have been proposed for multiple neurodegenerative diseases (Bossy-Wetzel et al., 2004). Most common hypotheses include interactions among neuroinflammation, oxidative stress, and excitotoxicity; mitochondrial dysfunction; alterations in calcium homeostasis; proteasomal dysfunction; protein aggregation; decrease in blood flow; alterations in blood–brain barrier, and neuronal cell cycle induction (Farooqui and Horrocks, 2007; Golde, 2009). However, placing these pathways in the proper relationship to the onset, time course, and progress of neurodegeneration and its relationship to cytoskeletal pathology are challenging issues that are not fully understood (Golde, 2009).

As stated above, the molecular mechanism of neurodegeneration in neurodegenerative diseases is very complex. These diseases progress slowly over time, often taking several years to reach the end stage. Does this observation mean that degenerating neurons yield to the disease only after a prolong agony or neurodegeneration occurs suddenly? Histochemical studies indicate that neurodegeneration corresponds to an asynchronous death, in that neurons within a neuronal population die at very different times with different rates. Thus, in a neurodegenerative disease at any given time, only a small number of neurons actually degenerate, while others are at various stages along the neuronal death pathway (Bossy-Wetzel et al., 2004; Ross and Poirier, 2004). This situation complicates clinical and biochemical measurements, which provide information on the entire population of cells in a particular brain region. Therefore, the rate of neurochemical alterations essentially reflects the changes in the entire population of affected cells in a particular brain region and provides very little insight into the pace at which the death of an individual neuronal cell occurs (Przedborski et al., 2003). Still, large body of in vitro data indicates that once a neuron becomes sick, the entire process of neurodegeneration proceeds control and prolonged clinical progression of neurodegenerative