

Contents

Chapter 1	Introduction	1
1.1	General Model for Protein Misfolding, Aggregation, Amyloid Formation and Neurodegeneration	1
1.2	Specificity of Molecular Mechanisms in Major Neurodegenerative Diseases	2
1.2.1	Alzheimer Disease (AD)	4
1.2.2	Parkinson Disease	4
1.2.3	Amyotrophic Lateral Sclerosis	6
1.2.4	Prions Diseases	6
1.3	Models of Amyloid Seeding in Neurodegenerative Diseases	8
	References	10
Chapter 2	Blood–Brain Barrier and Routes of Entry of Metal Ions into the Brain. Metal Ion Transport and Distribution in the Brain	12
2.1	General Features of Blood–Brain Barrier	12
2.2	Iron and Aluminium	14
2.3	Manganese	17
2.4	Lead and Mercury	19
2.5	The Olfactory Pathway of Metal Entry into the Brain	20
2.6	Astroglia and Metal Accumulation	20
	References	21
Chapter 3	Metal Ion-Induced Redox Reactions, Oxidative Stress and Possible Impact on Neurodegeneration	24
3.1	Metal Induced Production of ROS	24
3.2	Nitric Oxide	27
3.3	Oxidative Stress and Aging	29
3.4	ROS, Protein Oxidation and Aberrant Protein Interactions	29

3.5	Peroxidation of Lipids in Aging Brain	33
3.6	Impact of Oxidative Stress on DNA	33
3.7	ROS and Cell Death	34
	References	35
Chapter 4	Copper Metabolism in the Brain	39
4.1	Introduction	39
4.2	Models of Copper Metabolism	40
4.3	Mammalian Copper Homeostasis	44
4.4	Mammalian Cellular Copper Metabolism	45
4.5	Neurodegenerative Diseases and Copper	46
4.6	Wilson's and Menkes' Diseases	46
4.7	Familial Amyotrophic Lateral Sclerosis	51
4.8	Conclusions	52
	References	53
Chapter 5	Lithium, A Neuroprotective Element	57
5.1	IMPase	61
5.2	GSK-3	71
	References	80
Chapter 6	Neurotoxicity of Aluminium	83
6.1	Neurochemistry of Aluminium	83
6.2	Aluminum and the Etiology of Alzheimer's Disease	92
	References	94
Chapter 7	Manganese in the Brain Functioning	97
7.1	Introduction	97
7.2	Manganese Absorption	98
7.3	Manganese Transport to the Brain	99
7.4	Manganese Uptake in the Brain	101
7.5	Proteins that Utilise Manganese	103
7.6	Manganese Neurotoxicity	110
7.7	Effects on Brain Function	111
7.8	Neurological Disease Related to Manganese	111
7.9	Conclusions	113
	References	113

Chapter 8 Alzheimer's Disease: Which Metal Now?	117
8.1 Amyloid Precursor Protein	118
8.2 Cleavage of APP and Formation of β -Amyloid	120
8.3 Neurofibrillary Tangles	122
8.4 Copper, APP and A β	123
8.5 Metals and Alzheimer's Disease	125
8.6 A Balance Between Copper and Zinc	126
8.7 The Rise of Iron	129
8.8 Any More Metals in Alzheimer's Disease?	132
8.9 Coordination Chemistry of Metal Ions Interacting with APP	132
References	137
Chapter 9 Prion Diseases and Redox Active Metals	141
9.1 Introduction	141
9.2 Cu-Binding to PrP ^c	147
9.3 Details of Cu ²⁺ Co-Ordination to Mammalian PrP ^C and its Fragments	149
9.3.1 Binding of Cu ²⁺ Ion by a Single Octapeptide Repeat Pro-His-Gly-Gly-Gly-Trp-Gly-Gln	149
9.3.2 pH-Dependence of Cu ²⁺ Binding to Octapeptide Fragment	150
9.3.3 Binding of Cu ²⁺ Ions to Dimeric and Tetrameric Octapeptide Fragments	151
9.4 The Fifth and Sixth Binding Sites Located in <i>N</i> -Terminal Domain	155
9.5 Binding of Cu ²⁺ and Other Metals to PrP91–126 Region Cu(II) Coordination to PrP106–126 (KTNMKHMAGAAAAGAVVGLG)	156
9.5.1 Involvement of His-96 in the Interaction of Cu(II) with the Neurotoxic Peptide Fragment	158
9.5.2 The Comparison of the Binding Abilities of Octameric and Neurotoxic Regions Toward Cu ²⁺ Ions	158
9.6 Cu ²⁺ Coordination to Chicken PrP	160
9.7 Copper Mediated PrP Internalization	162
9.8 Copper Transport	166
9.9 PrP as an Antioxidant	167
9.10 Manganese Binding	170
9.11 Cell Death and Metals	171

9.11.1	Direct Effects	172
9.11.2	Indirect Effects	173
9.11.3	Combined Effects	173
9.11.4	Age Effects	173
9.12	Metal Changes in TSEs	174
9.13	Copper and Mutant Prions	176
9.14	Conclusions	176
	References	177
Chapter 10	Are Metals Involved in Cu–Zn Superoxide Dismutase-Related Familial Amyotrophic Lateral Sclerosis	182
	References	198
Chapter 11	Parkinson’s Disease: Any Role for Metals	201
11.1	Introduction	201
11.2	Cell Death in Parkinson’s Disease	202
11.3	Genetics of Parkinson’s Disease	203
11.4	The Proteins Associated with Parkinson’s Disease	205
11.4.1	Parkin	205
11.4.2	α -Synuclein	207
11.5	Metals in Parkinson’s Disease	211
11.6	Bioinorganic Chemistry in Parkinson Disease	213
11.6.1	Binding of Copper Ions to α -Synuclein and its Fragments	214
11.7	Metal Ions and Catecholamines	214
11.8	The Neuromelanin of Substantia Nigra and Metal Ions	217
11.9	Conclusions	218
	References	218
Chapter 12	Chelating Agents in Metal Neurotoxicity	223
12.1	Copper	227
12.2	Lead	230
12.3	Mercury	232
12.4	Iron	238
	References	242

<i>Contents</i>	xi
Chapter 13 Metal Complexes in the Brain Imaging and Diagnosis	244
13.1 Gadolinium Compounds	247
13.2 Monocrystalline Iron Oxide Nanocompounds	249
13.3 Delivery of MRI Contrast Agents	251
13.4 MRI Staining of the Hippocampal System	263
13.5 Contrast Agents in Stem Cells Therapy	266
13.6 Thallium Autoradiography	267
13.7 Targeting of Contrast Agents to AD Amyloid Plaques	267
References	274
Subject Index	277

