

Contents

Preface *xi*

Part I Neurotransmitter Systems 1

1	The Dopaminergic System	3
1.1	Introduction	3
1.2	Dopamine Receptors	5
1.2.1	Classification	5
1.2.2	Location	5
1.2.3	General Structural Considerations	6
1.2.4	Effector Mechanisms	8
1.2.5	Implication in Neurodisorders	9
1.2.6	D ₁ -like Receptors	9
1.2.7	D ₂ -like Receptors	12
1.3	Vesicular Monoamine Transporter (VMAT)	18
1.4	The Dopamine Transporter (DAT)	21
1.4.1	Structural Aspects	21
1.4.2	Molecular Mechanism	24
	References	26
2	The Noradrenergic System	41
2.1	Introduction	41
2.2	Adrenoreceptors	43
2.2.1	Classification	43
2.2.2	Location	44
2.2.3	General Structure Considerations	44
2.2.4	Effector Mechanisms	44
2.2.5	Implication in Neurodisorders	45
2.2.6	α ₁ -Adrenoreceptors	46
2.2.7	α ₂ -Adrenoreceptors	48
2.2.8	β-Adrenoreceptors	49
2.3	Neuropeptides Receptors	58
2.3.1	Neuropeptide Y Receptors	58

2.3.2	Galanin Receptors	61
2.4	Norepinephrine Transporter (NET)	63
	References	65
3	The Serotonergic System	81
3.1	Introduction	81
3.2	Serotonin Receptors	83
3.2.1	Classification	83
3.2.2	Location	86
3.2.3	General Structural Considerations	86
3.2.4	Effector Mechanism	87
3.2.5	Implication in Neurodisorders	88
3.2.6	5-HT ₁ Receptors	89
3.2.7	5-HT ₂ Receptors	92
3.2.8	5-HT ₃ Receptors	96
3.2.9	5-HT ₄ Receptors	98
3.2.10	5-HT ₅ Receptors	98
3.2.11	5-HT ₆ Receptors	100
3.2.12	5-HT ₇ Receptors	101
3.3	Serotonin Reuptake Transporter (SERT)	102
	References	107
4	The Cholinergic System	121
4.1	Introduction	121
4.2	Cholinergic Receptors	123
4.2.1	Classification	123
4.2.2	Location	124
4.2.3	Nicotinic Receptors	125
4.2.3.1	Effector Mechanisms	125
4.2.3.2	Implication in Neurodisorders	126
4.2.3.3	Structure of Subunits	126
4.2.3.4	Structure of Receptors	126
4.2.4	Muscarinic Receptors	132
4.2.4.1	Effector Mechanisms	133
4.2.4.2	Implication in Neurodisorders	134
4.2.4.3	M1 Receptor	134
4.2.4.4	M2 Receptor	135
4.2.4.5	M3 Receptor	135
4.2.4.6	M4 Receptor	139
4.2.4.7	M5 Receptor	141
4.3	Cholinergic Transporters	141
4.3.1	Vesicular Acetylcholine Transporter (VACHT)	141
4.3.2	High-Affinity Choline Transporter (ChT)	143
	References	145
5	The Glutamatergic System	155
5.1	Introduction	155
5.2	Glutamate Receptors	157

5.2.1	Classification	157
5.2.2	Ionotropic Receptors	159
5.2.2.1	Location	159
5.2.2.2	Effector Mechanisms	161
5.2.2.3	Implication in Neurodisorders	162
5.2.2.4	NMDA Receptors	162
5.2.2.5	AMPA Receptors	165
5.2.2.6	Kainate Receptors	168
5.2.2.7	Delta Receptors	172
5.2.3	Metabotropic Receptors	173
5.2.3.1	Location	173
5.2.3.2	Effector Mechanisms	174
5.2.3.3	Implication in Neurodisorders	175
5.2.3.4	Structural Features	176
5.3	Glutamate Transporters	184
5.3.1	Implication of Glutamate Transporters in Neurodegeneration	186
5.3.2	Vesicular Glutamate Transporter 1 (VGLUT1)	187
5.3.3	Vesicular Glutamate Transporter 2 (VGLUT2)	187
5.3.4	Vesicular Glutamate Transporter 3 (VGLUT3)	187
	References	188
6	The GABAergic System	199
6.1	Introduction	199
6.2	GABA Receptors	201
6.2.1	Classification	201
6.2.2	Location	201
6.2.3	Implication in Neurodegenerative Disorders	204
6.2.4	GABA _A Receptors	204
6.2.4.1	Effector Mechanisms	205
6.2.4.2	Structure of Subunits	206
6.2.5	GABA _B Receptors	210
6.2.5.1	Effector Mechanisms	210
6.2.5.2	Structure of Receptors	212
6.3	GABA Transporters	213
6.3.1	Vesicular GABA Transporter (VGAT)	216
6.3.2	Betaine Transporter (BGT1)	216
6.3.3	Sodium- and Chloride-Dependent GABA Transporters (GAT1–3)	216
	References	218
	Part II Metabolism and Proteins	227
7	Metabolism of Neurotransmitters	229
7.1	Introduction	229
7.2	Metabolism of Catecholamines	229
7.2.1	Dopamine	229
7.2.2	Norepinephrine (Noradrenaline) and Epinephrine (Adrenaline)	234

- 7.3 Metabolism of Serotonin 235
- 7.4 Metabolism of Acetylcholine 238
- 7.5 Metabolism of Glutamic Acid and GABA 239
 - 7.5.1 Glutamic Acid 239
 - 7.5.2 γ -Aminobutyric Acid (GABA) 240
 - 7.5.3 Neurotransmission Mediated by Glutamic Acid and GABA Metabolisms 240
 - References 242

- 8 Enzymes Processing Neurotransmitters 249**
 - 8.1 Tyrosine Hydroxylase (TH) 249
 - 8.2 Tryptophan Hydroxylase (Tryptophan-5-monoxygenase, TPH) 252
 - 8.3 Aromatic Amino Acid Decarboxylase (AADC) 255
 - 8.4 Dopamine β -Hydroxylase (DBH) 257
 - 8.5 Monoamine Oxidase (MAO) 259
 - 8.6 Catecholamine-O-methyl Transferase (COMT) 265
 - 8.7 Phenylethanolamine-N-methyl Transferase (PNMT) 270
 - 8.8 5-Hydroxyindole-O-methyltransferase (HIOMT) 272
 - 8.9 Serotonin-N-acetyl Transferase (SNAT) 274
 - 8.10 Choline Acetyltransferase (ChAT) 274
 - 8.11 Acetylcholinesterase (AChE) 276
 - 8.12 Glutamic Acid Decarboxylase (GAD) 280
 - 8.13 Glutamine Synthetase (GLUL) 281
 - 8.14 GABA Transaminase (GABA-T) 284
 - References 286

- 9 Misfolded Proteins 303**
 - 9.1 Introduction 303
 - 9.1.1 Amyloid β ($A\beta$) 304
 - 9.1.2 Tau (τ) 307
 - 9.1.3 α -Synuclein 313
 - References 316

- 10 Therapeutic Agents for Neurodegenerative Disorders 325**
 - 10.1 Alzheimer's Disease (AD) 325
 - 10.1.1 Acetylcholinesterase (AChE) Inhibitors 325
 - 10.1.2 Memantine (Namenda[®]) 331
 - 10.2 Parkinson's Disease (PD) 331
 - 10.2.1 L-DOPA 333
 - 10.2.2 Dopaminergic Agonists 335
 - 10.2.3 MAO-B Inhibitors 340
 - 10.2.4 COMT Inhibitors 343
 - 10.2.5 Amantadine 344
 - 10.3 Lewy Body Disease (LBD) 345
 - 10.4 Huntington's Disease (HD) 346

10.5	Friedreich's Ataxia (FA)	346
10.6	Amyotrophic Lateral Sclerosis (ALS)	346
10.7	Spinal Muscular Atrophy (SMA)	347
	References	347
	Index	359

