

Contents

Foreword xiii
Acknowledgments xv

Introduction 1

- 1. The life history of dopamine 5**
 - 1.1. A brief overview of the dopamine pathway 5
 - 1.2. A brief account of the blood-brain barrier 10
 - 1.3. Neurochemical anatomy of the nigrostriatal pathway 11
 - 1.4. Physiology of dopamine neurons 15
 - 1.5. The post-synaptic effects of dopamine 16
 - 1.6. A brief introduction to molecular imaging 17

- 2. Enzymology of tyrosine hydroxylase 19**
 - 2.1. Molecular biology and enzymology 19
 - 2.2. Disorders of tyrosine hydroxylase 20
 - 2.3. Regulation of activity 22
 - 2.4. Autoreceptor modulation of activity 24
 - 2.5. Phosphorylation of tyrosine hydroxylase 25
 - 2.6. Transcriptional regulation 27

- 3. The assay of tyrosine hydroxylase 29**
 - 3.1. Accumulation of DOPA after treatment with NSD 1015 29
 - 3.2. Superfusion of living striatum with [³H]tyrosine 34
 - 3.3. Intracerebroventricular infusion of [³H]tyrosine 36
 - 3.4. Intravenous injection of [³H]tyrosine 36
 - 3.5. Modeling the metabolism of [³H]tyrosine 37
 - 3.6. Autoradiography in vivo with tyrosine: an introduction to the analysis of PET data 40

x Contents

- 4. Enzymology of aromatic amino acid decarboxylase 45**
 - 4.1. Kinetic properties of AAADC in vitro 45
 - 4.2. Regulation and transcription of AAADC 48
 - 4.3. AAADC activity in living brain 50
 - 4.4. In vivo metabolism of AAADC substrates 51

- 5. PET studies of DOPA utilization 54**
 - 5.1. General aspects of the quantitation of FDOPA utilization 54
 - 5.2. Methods for the quantitation of DOPA-PET studies 57
 - 5.3. The true activity of AAADC in living brain 67
 - 5.4. Other substrates for PET studies of AAADC 68
 - 5.5. Pharmacological modulation of AAADC activity 69
 - 5.6. Clinical FDOPA-PET studies 71
 - 5.7. Personality and cognition 77

- 6. Conjugation and sulfonation of dopamine and its metabolites 80**
 - 6.1. Biochemistry of COMT 80
 - 6.2. Behavioral correlates of COMT activity 82
 - 6.3. Arylsulfotransferase 83

- 7. Dopamine synthesis and metabolism rates 85**
 - 7.1. Steady-state and the epistemology of dopamine metabolism 85
 - 7.2. Turnover of dopamine 86
 - 7.3. Turnover of the acidic metabolites 89
 - 7.4. 3-Methoxytyramine 95

- 8. MAO activity in the brain 99**
 - 8.1. Enzymology 99
 - 8.2. Neurochemical anatomy of MAO 101
 - 8.3. Effects of MAO inhibition and knockout on dopamine transmission 102
 - 8.4. Disorders of MAO and knockouts 103
 - 8.5. MAO activity in vivo 104
 - 8.6. Clinical PET studies of MAO 109

- 9. Vesicular storage of dopamine 111**
 - 9.1. Biochemistry of vesicular monoamine transporters 111
 - 9.2. Chromaffin granules 112

- 9.3. Regulating and knocking out VMAT2 114
- 9.4. Ligands and tracers for VMAT2 115
- 9.5. Clinical PET studies of VAT2 120

- 10. Dopamine release: from vesicles to behavior 122**
 - 10.1. Methods for measuring dopamine release 122
 - 10.2. Concentration gradients for dopamine across the plasma membrane 127
 - 10.3. The action of psychostimulants 128
 - 10.4. Behavioral correlates of dopamine release 131

- 11. The plasma membrane dopamine transporter 137**
 - 11.1. Molecular biology of DAT and regulation of expression 137
 - 11.2. Functional aspects of DAT, and how to live without it 138
 - 11.3. Ligands for the detection of DAT 141
 - 11.4. Clinical DAT studies 149

- 12. Dopamine receptors 160**
 - 12.1. Pharmacology and biochemistry 160
 - 12.2. Neurochemical anatomy 161
 - 12.3. Dopamine receptor signal transduction 163
 - 12.4. Agonist-induced internalization of dopamine receptors 165

- 13. Imaging dopamine D₁ receptors 167**
 - 13.1. General aspects of D₁ receptors 167
 - 13.2. PET ligands for D₁ receptors 168
 - 13.3. Imaging studies of D₁ receptors 171

- 14. Imaging dopamine D₂ receptors 174**
 - 14.1. General properties of D₂ ligands 174
 - 14.2. Oligomeric associations of dopamine D₂ receptors 180
 - 14.3. Effects of denervation on D₂ receptors 181
 - 14.4. Competitive binding at D₂ receptors in living brain 182
 - 14.5. Clinical studies of dopamine D₂ receptors 194

- 15. Factors influencing D₂ binding in living brain 203**
 - 15.1. Pharmacological modulation 203
 - 15.2. Clinical studies of psychostimulant-evoked dopamine release 205
 - 15.3. Other pharmacological challenges altering dopamine receptor binding 212

xii Contents

- 15.4. Transcranial magnetic stimulation, deep brain stimulation,
and sensory stimulation 215
- 15.5. Personality 217
- 15.6. Pain and stress 218
- 15.7. Motivation, craving, and placebo 220

- 16. The absolute abundance of dopamine receptors
in the brain 224**
- 17. Conclusions and perspectives 229**

References 234

Index 331

The color plates are between pages 28 and 29, and
pages 224 and 225.