

Contents

CHAPTER 13

Electrophysiological Pharmacology of Mesencephalic Dopaminergic Neurons

M. DIANA and J.M. TEPPER. With 6 Figures	1
A. Introduction	1
B. Anatomical Organization	2
C. Basic Electrophysiological Properties	4
I. Extracellular Recordings	4
II. Intracellular Recordings	7
D. Afferents to Dopaminergic Neurons	8
I. GABAergic Afferents	8
II. Glutamatergic Afferents	14
III. Cholinergic Afferents	19
IV. Monoaminergic Afferents	20
E. Autoreceptor-Mediated Effects on Dopaminergic Neurons	22
I. Somatodendritic Autoreceptors	22
II. Axon Terminal Autoreceptors	24
III. Are D ₂ Autoreceptors Different from Other D ₂ Receptors?	25
IV. Are Autoreceptors Ubiquitous Among Dopaminergic Neurons?	26
V. What Are the Physiological Roles of Autoreceptors?	28
F. Miscellaneous Neuropharmacology	31
I. Gamma-Hydroxybutyric Acid	31
II. Glycine	31
III. Neuropeptides	31
G. Acute and Chronic Effects of Antipsychotics on Dopaminergic Neurons	33

The first 12 chapters of this monograph are found in the companion volume (HEP 154/I). Its contents are reprinted immediately after those of the present volume.

I. Differences Between Effects of Typical and Atypical Antipsychotics	33
II. Effects of Chronic Antipsychotic Drug Administration – The Depolarization Block Hypothesis	34
H. Dopaminergic Neurons and Drugs of Abuse: Acute and Chronic Studies	36
I. Acute Effects of Drugs of Abuse on Dopaminergic Neurons	36
II. Chronic Effects of Drugs of Abuse on Dopaminergic Neurons	38
III. Withdrawal Following Chronic Administration	40
I. Conclusions	42
References	43

CHAPTER 14

Presynaptic Regulation of Dopamine Release

J. GLOWINSKI, A. CHÉRAMY, and M.-L. KEMEL. With 4 Figures	63
A. Introduction	63
B. Interactions Between Heteroreceptors or Heteroreceptors and D ₂ Autoreceptors Present on Dopaminergic Nerve Terminals	64
C. Role of Diffusible Messengers in the Presynaptic Control of Striatal Dopaminergic Transmission	67
D. Local Circuits Involved in the Control of DA Transmission in Striatal Compartments	70
I. Similarities and Differences in the Presynaptic Regulation of DA Release in Striatal Compartments	72
II. The GABA- and Dynorphin-Dependent Inhibitions of DA Transmission Triggered by Acetylcholine Occur in Two Distinct Matrix Territories	73
III. NMDA-Dependent Local Inhibitory Circuits of DA Transmission Occur in Both Striatal Compartments and Involve GABA and Dynorphin	74
IV. Facilitation by DA of the NMDA-Sensitive Local Inhibitory Circuits Involved in the Presynaptic Regulation of DA Release in Striatal Compartments	74
E. Conclusions	78
References	78

CHAPTER 15

Dopamine – Acetylcholine Interactions

E. ACQUAS and G. DI CHIARA. With 9 Figures	85
A. Introduction	85
B. Dopamine – Acetylcholine Interactions in the Basal Ganglia	85

Contents	XIII
I. Early Studies	86
II. Direct D ₁ Receptor-Mediated Facilitation of Striatal Acetylcholine Transmission	89
III. Separate Transduction Pathways for D ₁ and D ₂ Receptor-Mediated Influences on Acetylcholine Transmission	92
IV. Independent Gating of Input to Striatal Acetylcholine Neurons by Dopamine Receptor Subtypes	92
V. Relative Role of D ₁ and D ₂ Receptors in the Control of Striatal Acetylcholine Function	95
VI. Nicotinic Receptors and Dopamine Neurons	98
VII. Actions of Nicotine on Dopamine Function	98
VIII. Mechanism of Nicotine Actions on Dopamine Function	100
C. Dopamine – Acetylcholine Interactions Outside the Basal Ganglia	103
I. Dopaminergic Regulation of Cortical and Hippocampal Acetylcholine Transmission	104
References	105

CHAPTER 16

Dopamine – Glutamate Interactions

C. KONRADI, C. CEPEDA, and M.S. LEVINE. With 2 Figures	117
A. Introduction	117
B. Neuropharmacological Interactions	117
I. Dopamine and Glutamate Act Within the Same Neuronal Circuits	117
II. Dopamine and Glutamate Receptors in the Striatum	118
III. Reciprocal Release Regulation of Dopamine and Glutamate by Dopamine Receptors and Ionotropic Glutamate Receptors	119
IV. Reciprocal Regulation of Receptor Synthesis	120
V. Glutamate Regulates the Synthesis of Dopamine in Striatal Synaptosomes	120
VI. Glutamate and Dopamine Are Co-released from Dopamine Neurons	121
C. Intraneuronal Interactions	121
I. Dopamine Receptors and NMDA Receptors Cooperatively Modulate Gene Expression	121
D. Electrophysiological Interactions	122
I. Striatal Organization	122
II. Dopamine Modulates Glutamate Inputs	124
E. Interaction of the Dopamine and Glutamate Neurotransmitter Systems in Other Brain Areas	126

F. Functional Consequences of the Interaction of the Glutamate and Dopamine Systems	127
References	128

CHAPTER 17

Dopamine – Adenosine Interactions

M. MORELLI, E. ACQUAS, and E. ONGINI. With 2 Figures	135
A. Adenosine in the CNS	135
I. Receptor Distribution	135
II. Adenosine in CNS Pathology	137
B. Pharmacology of Adenosine Receptors	138
C. Adenosine – Dopamine Interactions	139
I. Dopamine D ₁ and Adenosine Receptors	140
II. Dopamine D ₂ and Adenosine Receptors	141
III. Modulation of Dopamine Release	143
D. Therapeutic Implications	144
References	145

CHAPTER 18

Dopamine – GABA Interactions

M.-F. CHESSELET	151
A. Introduction	151
B. The Anatomical Relationship Between Nigrostriatal Dopamine and GABAergic Neurons	151
I. Substantia Nigra	151
II. Striatum	152
III. Other Basal Ganglia Regions	152
C. Functional Interactions Between GABA and Nigrostriatal Dopaminergic Neurons	153
I. Striatum	153
1. Effects of GABA on Dopaminergic Neurons	153
2. Effects of Dopamine on GABAergic Output Neurons	153
3. Dopaminergic Regulation of Striatal GABAergic Interneurons	155
4. Dopaminergic Regulation of Striatal GABA Release ...	155
II. Dopamine – GABA Interactions in the Globus Pallidus ...	156
III. GABA – DA Interactions in the Internal Pallidum	158
IV. DA – GABA Interactions in the Substantia Nigra	159
V. Functional Implications of GABA – DA Interactions Within the Basal Ganglia	160

D. DA – GABA Interactions in the Mesolimbic Pathway 161
E. DA – GABA Interactions in the Mesocortical System 163
References 165

CHAPTER 19

Dopamine – Its Role in Behaviour and Cognition in Experimental Animals and Humans

T.W. ROBBINS and B.J. EVERITT. With 1 Figure 173

A. Introduction 173
B. Electrophysiological and Neurocomputational Approaches 174
C. Neuropharmacological Evidence for a Role for Dopamine in Learning 176
 I. Overview of Results from In Vivo Monitoring Studies 176
 II. Psychopharmacological Evidence of Specific Actions of Dopamine on Learning and Memory 178
 III. The Possible Complication of a Role for Dopamine in Attentional Function 182
 IV. Models of ADHD 185
D. Working Memory 186
 I. Problems of Interpretation of the Role of the PFC in Working Memory 190
E. Evidence for a Role for Dopamine in Cognition in Humans 192
 I. Dopamine and Cognition in Clinical Disorders: Parkinson’s Disease, Schizophrenia, Acute Brain Injury and ADHD 193
 II. Effects of Dopaminergic Drugs on Cognition in Normal Human Volunteers 196
F. Conclusions and Future Directions 199
References 203

CHAPTER 20

Molecular Knockout Approach to the Study of Brain Dopamine Function

G.F. KOOB, S.B. CAINE, and L.H. GOLD. With 6 Figures 213

A. Introduction 213
B. Limitations of the Knockout Approach: Compensation and Epistasis 216
C. Overview of the Midbrain Dopamine System in Motor Behavior and Reward 218
D. Overview of the Dopamine Receptor Subtypes in Motor Behavior and Reward 219
E. D₁ Receptor Knockouts 220

F. D ₂ Receptor Knockouts	222
G. D ₃ Receptor Knockouts	224
H. Knockout of the Dopamine Transporter	225
I. Knockout of Tyrosine Hydroxylase Gene	227
J. Other Knockouts	229
K. Summary and Conclusions: What We Know That We Did Not Know Before Knockouts	231
References	232

CHAPTER 21

**Behavioural Pharmacology of Dopamine D₂ and D₃ Receptors:
Use of the Knock-out Mice Approach**

R. DEPOORTERE, D. BOULAY, G. PERRAULT, and D.J. SANGER.

With 4 Figures	239
A. Introduction	239
B. Behavioural Pharmacology of DA D ₂ /D ₃ Receptor Agonists	240
C. Correlational Studies Using DA D ₂ /D ₃ Receptor Agonists	241
D. Behavioural Pharmacology of DA D ₂ /D ₃ Receptor Antagonists	242
E. Dopamine D ₃ Receptor Knock-out Mice	245
I. Analysis of the Phenotype of D ₃ Receptor Knock-out Mice	246
II. Effects of DA Receptor Ligands in D ₃ Receptor Knock-out Mice	246
1. DA D ₂ /D ₃ Receptor Agonists	247
2. DA D ₂ /D ₃ Receptor Antagonists	247
3. Psychostimulants	247
F. Dopamine D ₂ Receptor Knock-out Mice	247
I. Analysis of the Phenotype of D ₂ Receptor Knock-out Mice	248
II. Effects of DA Receptor Ligands in D ₂ Receptor Knock-out Mice	248
1. DA D ₂ /D ₃ Receptor Agonists	249
2. DA D ₂ /D ₃ Receptor Antagonists	249
3. Psychotropic Agents	249
G. Direct Comparison Between D ₂ and D ₃ Receptor Knock-out Mice	250
I. Comparison of Avoidance Behaviour of D ₂ and D ₃ Receptor Knock-out Mice	251
II. Comparison of Effects of DA Receptor Ligands in D ₂ and D ₃ Receptor Knock-out Mice	252
1. Psychotropic Agents	252
2. DA Receptor Antagonists	255

H. Conclusions	256
References	257

CHAPTER 22

Dopamine and Reward

G. DI CHIARA	265
A. Introduction	265
B. Terminology	266
I. Reward, Reinforcer, Incentive	267
II. Motivation and Instrumental Responding	268
1. Incentive-Motivational Responding	269
2. Instrumental Responding	270
C. Early Studies: The Original and the Revised Anhedonia Hypothesis	272
D. Testing the Original Anhedonia Hypothesis	274
I. Sweet Reward	274
II. Operant Responding for Sweet Reward	280
E. The Motor Deficit Issue	281
F. Response-Reinforcement Functions	285
I. Reward Summation Studies	285
II. Intensity-Threshold Studies	286
III. Response-Reinforcement Matching Studies	287
G. Dissociating Reinforcement from Incentive-Motivation and Performance	289
H. Incentive Accounts of the Role of Dopamine in Behaviour	291
I. Stimulus-Bound Incentive Role of Dopamine?	293
II. Dopamine and Incentive Arousal	294
III. Incentive Role of Drug-Stimulated Dopamine Transmission	295
I. Associative Learning Accounts	296
I. Pavlovian Incentive Learning	296
II. Place-Conditioning Studies	301
J. An Interpretative Framework of the Role of Dopamine in Reward	304
References	309

CHAPTER 23

Molecular and Cellular Events Regulating Dopamine Neuron Survival

G.U. CORSINI, R. MAGGIO, and F. VAGLINI	321
A. Introduction	321
B. Mechanisms of DA Cell Death	322
C. Extraneuronal Events	323

I. Noradrenergic System	323
1. NE in Experimental Parkinsonism	325
II. Excitatory Amino Acids	327
1. Excitotoxicity in PD	327
2. Excitotoxicity in Experimental Parkinsonism	329
3. The MPTP Model	329
a) Species Differences in MPTP Toxicity	331
b) MPP ⁺ Kinetics	332
c) Excitotoxicity in the MPTP Model	335
4. Methamphetamine Toxicity	336
5. 6-OHDA Toxicity	337
6. Conclusions on Excitotoxicity	339
III. Neurotrophic Factors	340
D. Intraneuronal Events	343
I. Oxidative Stress	343
II. Nitric Oxide	345
III. Apoptosis and Mitochondria	346
IV. Cytochrome P450 System	347
1. Cytochrome P450 in the CNS	348
2. P450 System and DA Neurons	349
a) CYP 2D6	350
b) CYP 2E1	351
3. The P450 System in PD	351
4. P450 in Experimental Parkinsonism	353
E. Toxicity of Dopamine	355
I. DA and Apoptosis	358
F. Conclusions About the Pathogenesis of PD	359
References	362

CHAPTER 24

Dopamine and Depression

P. WILLNER	387
A. Introduction	387
B. DA Function in Affective Disorders	389
I. DA Turnover	389
II. DA Receptors	391
III. Neuroendocrine Studies	392
IV. Summary	393
C. Mood Effects of DA Agonists and Antagonists	393
I. Psychostimulants	393
II. DA-Active Antidepressants	394
III. Neuroleptic-Induced Depression	396
IV. Parkinson's Disease	397
V. Neuroleptics as Antidepressants	397

VI. Summary	399
D. Dopaminergic Consequences of Antidepressant Treatment	399
I. DA autoreceptor Desensitization	399
II. Sensitization of D ₂ /D ₃ Receptors	400
III. Clinical Evidence	401
IV. Summary	402
E. Dopaminergic Mechanisms in Animal Models of Depression	402
I. D ₂ /D ₃ Receptor Sensitization as a Mechanism of Antidepressant Action	402
II. Clinical Evidence	404
III. Reciprocal Changes in DA Responses to Reward and Stress	404
IV. Summary	405
F. Conclusions	406
I. Limitations of the Dopamine Hypothesis	406
II. Syndromes or Symptoms?	407
III. The Wider Picture	408
References	409

CHAPTER 25

Dopamine in Schizophrenia

Dysfunctional Information Processing in Basal Ganglia – Thalamocortical Split Circuits

I. WEINER and D. JOEL. With 1 Figure	417
A. The Dopamine Hypothesis of Schizophrenia	417
B. Schizophrenia as a Dopamine-Dependent Dysfunctional Information Processing in Basal Ganglia – Thalamocortical Circuits	423
I. Circuit Models of Schizophrenia	425
II. The Split Circuit Model of Schizophrenia	428
1. Striatum as a Contention Scheduling Device	430
2. The Interaction Between the Striatum and the Frontal Cortex	432
3. Contention Scheduling of Goals by the Limbic Striatum	433
4. The Role of Tonic and Phasic DA in the Contention Scheduling of Goals	433
a) Tonic and Phasic DA Release	434
b) The Establishment of Goals in the Limbic Striatum	436
c) Goal Selection	436
d) Goal Maintenance and Energizing	437
e) Switching Between Goals	438
5. The Translation of Goals to Behavior	439

6. Schizophrenia	440
a) Fronto-temporo-limbic Cortical Dysfunction and Dysregulation of Tonic and Phasic DA Transmission in Schizophrenia	442
b) The Consequences of Fronto-temporo-limbic Cortical Dysfunction: Disrupted Establishment of Goals	442
c) The Consequences of Dysregulation of the DA Input to the Limbic Striatum	444
α) Reduced Tonic DA: Goal Selection, Activation and Maintenance	444
β) Abnormal Phasic DA Release: Learning and Switching	446
d) Summary: Phasic and Tonic DA Dysregulation and Schizophrenia Symptoms	449
References	451

CHAPTER 26

Atypical Antipsychotics

J.E. LEYSEN. With 1 Figure	473
A. Introduction	473
B. Receptor Binding Profile of Antipsychotics	474
C. Interaction with Dopamine Receptors	481
D. Interaction with 5-HT ₂ and Other 5-HT Receptors	483
E. Interaction with Various Biogenic Amine Receptors	484
F. Future Antipsychotics	485
G. Conclusions	486
Abbreviations	487
References	487

CHAPTER 27

Sleep and Wake Cycle

J. BIERBRAUER and L. HILWERLING	491
A. Introduction	491
B. Dopaminergic Action in Sleep	492
I. D ₂ Antagonists	492
II. D ₂ Agonists	493
III. D ₁ Antagonists	494
IV. D ₁ Agonists	494
V. More Specific Studies	494
VI. Catecholaminergic Pathway Modulation	495
VII. Temperature Regulation	495

C. Pharmacological Interactions	496
I. Serotonin	496
II. Adrenergic System	497
III. Acetylcholine	498
IV. Histamine	498
1. H ₁ Receptor	499
2. H ₂ Receptor	499
3. H ₃ Receptor	499
V. GABAergic System	499
D. Summary	500
References	501
Subject Index	507