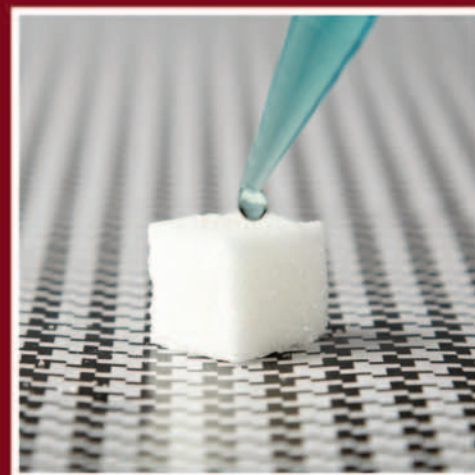


Neuropathology of
**DRUG ADDICTIONS
AND SUBSTANCE MISUSE**

**Stimulants, Club and
Dissociative Drugs,
Hallucinogens, Steroids,
Inhalants and
International Aspects**



EDITED BY VICTOR R. PREEDY

VOLUME 2



Neuropathology of Drug Addictions and Substance Misuse

Volume 2: Stimulants, Club and Dissociative Drugs,
Hallucinogens, Steroids, Inhalants, and International Aspects



ELSEVIER *science & technology books*

•• Companion Web Site:

<http://booksite.elsevier.com/9780128002124>

Neuropathology of Drug Addictions and Substance Misuse, Volume 2
Victor R. Preedy, Editor

Available Resource:

- Additional Resources and Recommended Reading



ACADEMIC
PRESS

Neuropathology of Drug Addictions and Substance Misuse

Volume 2: Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants, and International Aspects

Edited by

Victor R. Preedy

King's College London, London, UK



ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON • NEW YORK • OXFORD • PARIS
SAN DIEGO • SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Academic Press is an imprint of Elsevier



Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, UK
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA
50 Hampshire Street, 5th Floor, Cambridge, MA, 02139, USA
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

Copyright © 2016 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-800212-4

For information on all Academic Press publications
visit our website at <https://www.elsevier.com/>



Working together
to grow libraries in
developing countries

www.elsevier.com • www.bookaid.org

Publisher: Mara Conner

Acquisition Editor: Mara Conner

Editorial Project Manager: Kathy Padilla

Production Project Manager: Julia Haynes

Designer: Matt Limbert

Typeset by TNQ Books and Journals

www.tnq.co.in

Contents

List of Contributors	xxv
Preface	xxxv
Acknowledgments	xxxvii

Part I Stimulants

Section A General Aspects

1. Cocaine: Usage, Misuse, and Addiction Processes. An Overview

Derek P. Simon and Mary Jeanne Kreek

Introduction	5
Clinical Perspectives on Cocaine Abuse	5
Molecular Neurobiology of Cocaine Addiction	7
Conclusions	9
Applications to Other Drugs of Abuse	9
Definition of Terms	10
Key Facts of the Statistics of Cocaine Use in the United States	10
Summary Points	10
References	10

2. Amphetamine Usage, Misuse, and Addiction Processes: An Overview

Nicola Simola and Manolo Carta

Introduction	14
Usage, Misuse, and Addiction Processes	14
Definition of Terms	21
Key Facts	22
Summary Points	22
References	22

3. Mephedrone

Mariana Angoa-Pérez and Donald M. Kuhn

Introduction	25
β -Ketoamphetamines, Amphetamines and the Potential for Neurotoxicity	25

Strategy for Examination of the Neurotoxic Potential of Mephedrone	26
Mephedrone Does Not Damage DA Nerve Endings	26
Mephedrone Enhances the Neurotoxicity Caused by Methamphetamine, Amphetamine, and MDMA	29
Mephedrone Does Not Damage 5HT Nerve Endings	30
Discussion	30
Applications to Other Addictions and Substance Misuse	32
Definition of Terms	32
Key Facts of Mephedrone Abuse	33
Summary Points	33
References	33

Section B Molecular and Cellular Aspects

4. Cocaine and Brain-Derived Neurotrophic Factor

Lisia von Diemen, Giovana Brolese, Marianne Possa, Silvia Bassani Schuch and Anne Orgler Sordi

Introduction	39
BDNF, Cocaine, and Animal Models	39
BDNF Genetics in Cocaine Addiction	41
Clinical Studies and BDNF	42
Applications to Other Addictions and Substance Misuse	44
Definition of Terms	44
Key Facts of Cocaine and BDNF	45
Summary Points	45
References	45

5. On the Role of the Endocannabinoid System in Cocaine Addiction

Przemysław Adamczyk and Mariusz Papp

Introduction	48
Overview of the ECBS	48
ECBS in Cocaine Addiction	50

Conclusions	53	Key Facts	83
Applications to Other Addictions and Substance Misuse	57	Summary Points	83
Definition of Terms	57	Acknowledgment	84
Key Facts of Self-Administration	59	References	84
Summary Points	60		
References	60		
6. The Fas Receptor/Fas-Associated Protein and Cocaine		8. Metabotropic Glutamate 5 Modulators: Potential Agents for Treating Cocaine Addiction	
<i>M. Julia García-Fuster, María Álvaro-Bartolomé and Jesús A. García-Sevilla</i>		<i>Christina J. Perry and Andrew J. Lawrence</i>	
Introduction	63	Introduction: Addressing the Need for Treating Cocaine Abuse	86
Relevant Features of Fas Receptor and FADD Adaptor	64	mGlu5 Receptor: A Brief Background	87
Regulation of Fas Receptor Forms by Cocaine	66	The Cycle of Developing Addiction	87
Regulation of FADD Forms by Acute and Chronic Cocaine in Rat Brain	66	The Incentive Value of Cocaine	88
Role of FADD Forms in the Initial Propensity to Cocaine Use	67	Repeated Cocaine Exposure Leads to Sensitization to the Effects of Cocaine	89
Regulation of FADD Forms in Human Cocaine Addiction	68	Cocaine Use Escalates with Exposure	89
Relevance of Fas/FADD Regulation by Cocaine and Its Downstream Signaling	69	Withdrawal and Relapse	90
Conclusions	69	Withdrawal Creates an Incubation of Craving	90
Applications to Other Addictions and Substance Misuse	70	Extinguished Cocaine-Seeking Is Readily Reinstated	91
Definition of Terms	70	Two Approaches to Treating Cocaine Dependence	92
Key Facts	70	Applications to Other Addictions and Substances Misuse	93
Summary Points	71	Conclusion	93
Acknowledgments	71	Definition of Terms	93
References	71	Summary Points	94
		Acknowledgment	94
		References	94
7. Cocaine and Neuromolecular Imaging of Neurotransmitters in the Brain: BRODERICK PROBE® Laurate Nanobiosensors in Mesocorticolimbic Neurons and the Nucleus Accumbens: Sex and Genes		9. Neuronal and Behavioral Effects of Amphetamine in <i>Caenorhabditis elegans</i>	
<i>Patricia A. Broderick</i>		<i>Lucia Carvelli</i>	
Introduction	74	Introduction	97
Cocaine is a Psychostimulant	75	<i>Caenorhabditis elegans</i> Homologies with Mammalian Dopaminergic Synapses	98
Role of NMI in the Study of Cocaine	75	Amphetamine Directly Modulates the Dopaminergic Neurons	99
Sexual Dimorphism in Cocaine-Induced Neurochemistry Online with Behavior	78	Amphetamine Causes Behavioral Effects in <i>Caenorhabditis elegans</i>	100
Role of the Estrous Cycle in Cocaine-Induced Responses	79	Amphetamine Activates Targets Other than the Dopaminergic System to Generate Behavioral Effects	102
Role of the Genetic FH Animal Model of Depression in Cocaine Addiction: Comparison with the SD Strain	80	β -Phenylethylamine and Amphetamine Activate the Same Molecular Targets but via Different Kinetics	102
Applications to Other Addictions and Substance Misuse	82	Application to Other Addictions and Substance Misuse	104
Definition of Terms	83	Definition of Terms	104
		Key Facts	104
		Summary Points	105
		References	105

10. Amphetamines Activate G-Protein Coupled Trace Amine-Associated Receptor 1 (TAAR1): Implications for Understanding and Treating Psychostimulant Abuse			
<i>David K. Grandy</i>			
Introduction	108		
Discovery of the Trace Amine Receptor	109		
Anatomic Localization	110		
Pharmacologic Characterization of the Trace Amine Receptor	110		
Drug Development Programs	110		
In Vivo Studies Related to Drug Abuse	112		
Future Directions	113		
Applications to Other Addictions and Substance Misuse	113		
Definition of Terms	113		
Key Facts about TAAR1	114		
Summary Points	114		
References	114		
11. Amphetamine and Signal Detection			
<i>Matthew E. Andrzejewski and Nicole Holder</i>			
Introduction	117		
A Primer on Signal Detection Theory	117		
Sensitivity Indices: d' , A' , SI , and Percent Correct	120		
AMPH Effects on Sensitivity	120		
Terminology and Experimental Procedures	121		
Dose Effects of AMPH	122		
Implications of AMPH Effects on Signal Detection	122		
Conclusions	122		
Applications to Other Addictions and Substance Misuse	122		
Definition of Terms	123		
Key Facts on AMPH and Signal Detection	123		
Summary Points	123		
References	124		
Further Reading	124		
12. The Effects of Amphetamine and Methamphetamine on Brain Activity-Related Immediate Early Gene Expression			
<i>Peter R. Kufahl, Elisabeth Moore and M. Foster Olive</i>			
Introduction	126		
Applications to Other Addictions and Substance Misuse	133		
Conclusions	133		
Definition of Terms	134		
Key Facts	134		
Summary Points	134		
References	134		
Summary Points		134	
References		135	
13. Methamphetamine-Induced Behavioral Abnormalities and Neuronal Apoptosis			
<i>Tomohiro Abekawa</i>			
Introduction	137		
METH-Induced Psychosis	137		
METH-Induced Neurotoxicity	138		
Models for METH-Induced Psychosis	138		
Neurodevelopmental Deficits and METH-Induced Psychosis and Apoptosis	141		
Conclusions	142		
Applications to Other Addictions and Substance Misuse	143		
Definition of Terms	143		
Key Factors of METH-Induced Apoptosis	144		
Summary Points	144		
Acknowledgment	144		
References	144		
14. Methamphetamine and the JAK/STAT Pathway			
<i>Joana Gonçalves and Ana Paula Silva</i>			
The JAK/STAT Signaling Pathway in the Central Nervous System: An Overview	147		
JAK/STAT Pathway and Methamphetamine	149		
Applications to Other Addictions and Substance Misuse	151		
Definition of Terms	151		
Key Facts	152		
Summary Points	153		
References	153		
15. Methamphetamine and the Blood–Brain Barrier			
<i>Ricardo Alexandre Leitão, Vanessa Coelho-Santos and Ana Paula Silva</i>			
BBB Composition and Function: A Quick Overview	155		
Effect of METH on BBB Function: Causes and Consequences	157		
Adhesion Molecules and Transendothelial Immune Cells Migration	159		
METH Abuse and Brain Infection	159		
Conclusions	161		
Applications to Other Addictions and Substance Misuse	165		
Definition of Terms	165		
Key Facts	166		
Summary Points	166		
References	166		

16. Melatonin Receptors as Modulators of Methamphetamine-Mediated Behaviors

Shannon J. Clough, Anthony J. Hutchinson and Margarita L. Dubocovich

Introduction	169
Methamphetamine	169
Melatonin Receptors	170
The Circadian Clock and Drugs of Abuse	170
Locomotor Sensitization	170
Conditioned Place Preference	174
Conclusions	177
Applications to Other Addictions and Substance Misuse	177
Definition of Terms	177
Key Facts	177
Summary Points	178
References	178

17. Methamphetamine Neurotoxicity and the Ubiquitin–Proteasome System

Anna Moszczynska

Introduction	181
The Proteasome in Methamphetamine Neurotoxicity	182
The E3 Ligase Parkin in Methamphetamine Neurotoxicity	182
Summary and Conclusions	184
Applications to Other Addictions and Substance Misuse	185
Definition of Terms	186
Key Facts	186
Summary Points	186
References	187

18. Methamphetamine and Neuronal Nitric Oxide

Chitra D. Mandyam

Definition of Neurotoxicity and Preclinical Models of Methamphetamine Neurotoxicity	189
Definition of Addiction, the Stages of Addiction and Animal Models of Methamphetamine Addiction	189
Methamphetamine Neurotoxicity	189
Nitric Oxide, a Neurotransmitter with Two Faces	190
Role of Nitric Oxide in Methamphetamine Neurotoxicity	191
Applications to Other Addictions and Substance Misuse	193
Definition of Terms	193

Key Facts about Methamphetamine and nNOS	193
Summary Points	193
Acknowledgments	193
References	193

19. Candidate Genes of Chromosome 18q21, Methamphetamine, and Psychosis

Byung Dae Lee

Introduction	196
Applications to Other Addictions and Substance Misuse	203
Definition of Terms	203
Key Facts	203
Summary Points	203
References	204

Section C Structural and Functional Aspects

20. Structural and Functional Aspects of Stimulant Misuse and Addiction

Alfonso Barrós-Loscertales

Introduction	209
Striatum and Midbrain	210
Structural and Functional Alterations of the Prefrontal Cortex in Stimulant Addiction and Misuse	210
Structural and Functional Alterations in Other Brain Regions	213
Functional and Structural Connectivity	214
Conclusions	215
Applications to Other Addictions and Substance Misuse	216
Definition of Terms	216
Key Facts about Aspects of Stimulant Misuse and Addiction	216
Summary Points	216
References	217

21. Sleep and Cocaine

Gustavo A. Angarita, Sofija V. Canavan, Sarah E. Hodges and Peter T. Morgan

Introduction	220
Subjective Measurements	220
Objective Measurements	221
Relationship between Subjective and Objective Sleep Outcomes	222
Relationship between Sleep Outcomes and Cognition	222
Relationship between Sleep Outcomes and Mood	223
Sleep and Cocaine Use Outcomes	223

Neurobiology of Cocaine-Induced Sleep Changes	223		
Pharmacotherapy Options Targeting Sleep Abnormalities	223		
Psychotherapy Options for the Treatment of Sleep Problems in Cocaine Users	225		
Applications to Other Addictions and Substance Abuse	225		
Definition of Terms	225		
Key Facts about Subjective and Objective Assessments of Sleep	226		
Summary Points	226		
References	226		
22. Motivations for Use of Crack Cocaine			
<i>Alissa M. Greer, Gina Martin, Chantele Joordens and Scott Macdonald</i>			
Introduction	229		
Cocaine and Cocaine Dependence	229		
Route of Administration	230		
Neurological Basis of Motivations to Use Cocaine	231		
Pavlovian Cue-Induced Cravings and Instrumental Behavior	231		
Social Factors and Measuring Motivations for Cocaine Use	232		
Research Findings	233		
Motivations for Use in a Mainly Cocaine-Using Population	233		
Applications to Other Addictions and Substance Misuse	234		
Definition of Terms	234		
Key Facts	235		
Summary Points	235		
References	235		
23. Cocaine and Postmortem Levels in Neurological Tissues			
<i>Eduardo Alvear Serrano, Dietrich von Baer, Claudia Mardones and Carola Vergara Rosales</i>			
Introduction	237		
Applications to Other Addictions and Substance Misuse	238		
Presentation of the Problem	238		
COC and BZE Concentrations in Neurological Tissues and Other Matrices	239		
Postmortem Distribution of COC and BZE in Neurological Tissues	240		
Definition of Terms	242		
Key Facts of Cocaine Abuse	243		
Summary Points	243		
References	243		
24. Cerebral Gray Matter Volumes in Cocaine Dependence: Clinical and Functional Implications			
<i>Chiang-Shan R. Li</i>			
Neuroinflammatory and Vasoactive Effects of Cocaine	245		
Key Facts	253		
References	253		
25. The Rise of the Ego: Social Cognition and Interaction in Cocaine Users			
<i>Boris B. Quednow</i>			
Introduction	257		
The Zurich Cocaine Cognition Study	258		
Basal Cognitive Functions	258		
Color Vision and Early Information Processing	259		
Social Cognition and Interaction	260		
Applications to Other Substance Addictions and Misuses	264		
Conclusion	265		
Definition of Terms	265		
Key Facts of Cocaine Use	266		
Summary Points	266		
Acknowledgments	266		
References	266		
26. Amphetamine-Induced Psychosis			
<i>Vahid Farnia and Senobar Golshani</i>			
Introduction	269		
Clinical Features	270		
Functional and Structural Aspects	272		
Treatment	275		
Applications to Other Addictions and Substance Misuse	277		
Definition of Terms	277		
Key Facts	277		
Summary Points	278		
References	278		
27. The Role of Environmental Context in Amphetamine Abuse			
<i>Daniela F. Fukushiro, Laís F. Berro, Renan Santos-Baldaia, André W. Hollais and Raphael Wuo-Silva</i>			
Introduction	281		
Applications to Other Addictions and Substance Misuse	287		
Definition of Terms	288		
Key Facts	288		
Summary Points	288		
References	289		

28. Adolescent Exposure to Amphetamines and Vulnerability to Addiction

Emily R. Hankosky and Joshua M. Gulley

Adolescence: A Time of Change	292
Behavioral Antecedents of Adolescent Amphetamine (AMPH) Use	292
Neurobiological Precursors of Adolescent Use of AMPHs	293
Adolescents and AMPHs: Use and Abuse	293
Adolescence: A Time of Heightened Vulnerability?	294
Applications to Other Addictions and Substance Misuse	296
Call to Action	296
Definition of Terms	297
Key Facts of Adolescence	297
Summary Points	297
References	298

29. The Effect of Oxytocin on Methamphetamine Addiction

Chun-Fu Wu, Jing-Yu Yang and Fang Wang

Introduction	300
Applications to Other Addictions and Substance Misuse	305
Definition of Terms	305
Key Facts about Microdialysis	306
Summary Points	306
References	306

30. Peripheral Influences of Methamphetamine Neurotoxicity

Amanda L. Blaker, Nicole A. Northrop and Bryan K. Yamamoto

Introduction	309
Central Nervous System Effects of Methamphetamine	309
Peripheral Contributors to METH Toxicity	310
Implications	314
Conclusions	315
Applications to Other Addictions and Substance Misuse	316
Definition of Terms	316
Key Facts about Methamphetamine	316
Summary Points	317
Acknowledgments	317
References	317

31. Methamphetamine-Induced Hyperlocomotion

Yukio Ago, Kazuhiro Takuma and Toshio Matsuda

Introduction	320
METH-Induced Hyperactivity	320
The Role of Prefrontal Monoamine Systems in METH-Induced Hyperactivity	320
Chronic Administration of METH	322
The Role of the Prefrontal Serotonergic System in METH-Induced Behavioral Sensitization	322
Conclusion	325
Applications to Other Addictions and Substance Misuse	325
Definition of Terms	326
Key Facts of Serotonergic System	326
Summary Points	326
References	326

32. ¹H-Magnetic Resonance Spectroscopy and Methamphetamine

Fleur Margaret Howells

Introduction	329
Use of ¹ H-MRS to Study Effects of Methamphetamine Use	329
Applications to Other Addictions and Substance Misuse	333
Definition of Terms	333
Key Facts	334
Summary Points	334
References	334

33. Neuropsychological Aspects of Methamphetamine Use Disorders and Human Immunodeficiency Virus Disease

Erin E. Morgan, Jennifer E. Iudicello, Erica Weber and Steven Paul Woods

Epidemiology of Methamphetamine and Human Immunodeficiency Virus	336
Methamphetamine	336
Human Immunodeficiency Virus	338
Combined Effects of MA and HIV	339
Special Topics	341
Applications to Other Addictions and Substance Misuse	342
Definition of Terms	342
Key Facts	342
Summary Points	343
References	343

Section D Methods

34. Quantitative Colorimetric Assays for Methamphetamine

Aree Choodum and Niamh NicDaeid

Introduction	349
Colorimetric Assays for MA	350
Quantification of MA by Colorimetric Assay	352
Applications to Other Addictions and Substance Misuse	355
Conclusions	355
Definition of Terms	356
Key Facts	357
Summary Points	358
References	358

35. Assays for Methamphetamine and Amphetamine in Blood

Takeshi Kumazawa

Introduction	360
Chromatographic Methods for Methamphetamine and Amphetamine	360
Internal Standards for Quantitative Analysis of Methamphetamine and Amphetamine	366
Extraction Method for Methamphetamine and Amphetamine in Human Blood	366
Conclusion	369
Applications to Other Addictions and Substance Misuse	369
Definition of Terms	370
Key Facts	371
Summary Points	371
References	372

Part II Club Drugs

Section A General Aspects

36. Gamma-Hydroxybutyrate Abuse and Dependence

Martijn van Noorden, Rama Kamal, Boukje Dijkstra, T.M. Brunt and Cor de Jong

General Aspects	379
Molecular and Cellular Aspects	380
Structural and Functional Aspects	383

Applications to Other Addictions and

Substance Misuse	385
Definition of Terms	385
Summary Points	385
References	386

Section B Molecular and Cellular Aspects

37. Effects of Club Drugs on Dopaminergic and Serotonergic Systems: Use of [¹⁸F] FDOPA, [^{99m}Tc]TRODAT-1, and [I*] ADAM

Skye Hsin-Hsien Yeh, Chun-Kai Fang and Jeng-Jong Hwang

Introduction	391
Club Drugs and Their Imaging Applications	393
Methamphetamine	393
Ketamine	395
Advanced Multimodalities of Molecular Imaging: PET versus QAR	395
Neuroimaging with Selected Radiotracers	395
Imaging of DA Synthesis	397
Imaging of SERTs with [I*]ADAM	399
Conclusions	401
Applications to Other Addictions and Substance Misuse	401
Definition of Terms	401
Key Facts	401
Summary Points	401
Acknowledgments	402
References	402

38. MDMA and Glutamate

John H. Anken, Stuart A. Collins, Bryan K. Yamamoto and Gary A. Gudelsky

Introduction	406
Mechanisms of MDMA 5-HT Toxicity	407
MDMA and Gamma-Aminobutyric Acid Toxicity	407
MDMA and Hippocampal Glutamate	408
Potential Consequences of MDMA GABA Toxicity	409
Conclusion	410
Applications to Other Addictions and Substance Misuse	410
Definition of Terms	411
Key Facts About MDMA Abuse	411
Summary Points	412
References	412

39. MDMA (Ecstasy) and Gene Expression in the Brain: An Overview of Microarray and Candidate Gene Studies Assessing Transcriptional Changes in Rodents

Noelia Fernández-Castillo, Marta Ribasés and Bru Cormand

Introduction	415
Acute MDMA Administration	417
Repeated and Chronic MDMA Administration	420
MDMA Self-Administration	424
Prenatal Exposure to MDMA	424
Molecular and Cellular Events Triggered by Exposure to MDMA	424
Application to Other Addictions and Substance Misuse	426
Definition of Terms	426
Key Facts	427
Summary Points	428
References	428

40. Mitochondrial Trails in the Neurotoxic Mechanisms of MDMA

Daniel José Barbosa, João Paulo Capela, Maria de Lourdes Bastos and Félix Carvalho

Introduction	431
Mitochondrial Electron Transport Chain Function	431
The Outer Mitochondrial Membrane Enzyme MAO	434
Mitochondrial Fusion/Fission	436
Neuronal Mitochondrial Trafficking	436
Mitochondrial Regulators and Apoptotic Pathways	437
Concluding Remarks	440
Applications to Other Addictions and Substance Misuse	440
Key Facts about Mitochondria	440
Summary Points	440
References	442

41. Flunitrazepam–Membrane Binding

Anahí V. Turina, Daniel A. García and Maria A. Perillo

Introduction	445
Conclusions	449
Applications to Other Addictions and Substance Misuse	449
Definition of Terms	450
Key Facts About FNZ Binding	450

Summary Points	450
Acknowledgment	450
References	450

42. Neurotoxicity due to Repeated Comas Following Excessive Use of Gamma-Hydroxybutyric Acid

J.G.C. van Amsterdam, T.M. Brunt, M.T.B. McMaster and W. van den Brink

Introduction	453
Mode of Action	453
Intoxications and Coma	454
GHB-Induced Neurotoxicity	455
GHB, General Anesthesia, and Neurotoxicity	455
Other Sedative Substances	456
Discussion	456
Accountability	457
Applications to Other Addictions and Substance Misuse	457
Definition of Terms	457
Key Facts	457
Summary Points	457
References	457

Section C Structural and Functional Aspects

43. The Behavioral Effects of MDMA in Humans Under Controlled Laboratory Conditions

Matthew Kirkpatrick, Casey Guillot and Carl Hart

Introduction	463
MDMA's Chemical Structure and Mechanism of Action	463
A Brief History of MDMA Use and Legal Control	464
Concerns About MDMA Use	464
Human Behavioral Pharmacology	
Studies of Acute MDMA Effects	465
Physiological Effects	465
Subjective Effects	466
Psychomotor and Cognitive Performance on Standardized Computer Tasks	468
Effects on Social and Emotional Processing and Social Behavior	468
Conclusion	469
Applications to Other Addictions and Substance Misuse	470
Definition of Terms	470
Key Facts About MDMA and its Recreational Use	470

Summary Points	470	Summary Points	497
References	471	References	497
44. Recreational Use of Ecstasy (MDMA) and Hippocampal Memory			
<i>Christian Montag and Benjamin Becker</i>			
Introduction	473		
Acute Pharmacology of MDMA and Potential Harmful Effects on the Serotonergic System	473		
Challenges in the Investigation of Human Recreational Ecstasy Users	474		
Neuropsychological Findings in Recreational Ecstasy Users	475		
Imaging and Molecular Genetic Imaging Perspectives	476		
Applications to Other Addictions and Substance Misuse	480		
Conclusions	480		
Definition of Terms	480		
Key Facts of Recreational Ecstasy Use	480		
Summary Points	481		
Acknowledgments	481		
References	481		
45. Catalepsy and Comparing Gamma-Hydroxybutyrate, 1,4-Butanediol, and Gamma-Butyrolactone			
<i>Siripan Phattananudee, Timothy J. Maher and Pasarapa Towiwat</i>			
Introduction	484		
Applications to Other Addictions and Substance Misuse	487		
Definition of Terms	488		
Key Facts of GHB as a Substance of Abuse	488		
Summary Points	489		
References	489		
46. Epidemiology of Gamma-Hydroxybutyrate (GHB) Use and Misuse and Characteristics of GHB-Dependent Inpatients			
<i>T.M. Brunt, Martijn van Noorden, Rama Kamal, Boukje Dijkstra and Cor de Jong</i>			
General Aspects	491		
Characteristics of GHB Use	492		
Characteristics of GHB-Dependent Inpatients	494		
Applications to Other Addictions and Substance Misuse	496		
Definition of Terms	497		
		Section D	
		Methods	
		47. Assays for MDMA and Its Metabolites	
		<i>Bardia Jamali, Meshkat Torkamania, Nima Badri, Behjat Sheikholeslami, Yalda Hosseinzadeh Ardakani and Mohammad-Reza Rouini</i>	
		Introduction	503
		Matrices	503
		Sample Preparation	505
		Analytical Instruments for the Determination of MDMA and Its Metabolites	506
		Conclusion	508
		Applications to Other Addictions and Substance Misuse	508
		Definition of Terms	509
		Key Facts of MDMA	509
		Summary Points	509
		References	509
		48. Assays for Flunitrazepam	
		<i>Béla Kiss, Ede Bodoki, Anca Pop and Felicia Loghin</i>	
		Samples and Analytes	514
		Sample Preparation	515
		Analytical Techniques	517
		LC-DAD	524
		LC-MS and LC-MS/MS	524
		Capillary Electrophoresis and Capillary Electrochromatography	525
		Applications to Other Addictions and Substance Misuse	526
		Definition of Terms	526
		Key Facts about Conjugated Metabolites Hydrolysis	526
		Summary Points	526
		References	526
		49. Detection of GHB by Optical Methods	
		<i>Wang Xu, Duanting Zhai and Young-Tae Chang</i>	
		Introduction	529
		A Colorimetric Sensor Array for the Detection of GHB	530
		A Fluorescent Sensor for the Detection of GHB	530
		Commercial Kits for the Detection of GHB	532
		A Fluorescent Sensor for the Prodrug of GHB-GBL	533

Conclusion	533
Applications to Other Addictions and Substance Misuse	533
Definition of Terms	534
Key Facts of GHB and GBL Optical Sensors	534
Summary Points	534
References	535

Part III Dissociative Drugs

Section A

General Aspects

50. Ketamine Analgesia

Linda C.J. Oudejans, Monique van Velzen and Albert Dahan

Introduction: History and Recent Interest	541
Chemistry and Pharmacology	542
Ketamine for Treatment of Acute and Chronic Pain	543
Implications for Drug Addictions and Substance Misuse	546
Applications to Other Addictions and Substance Misuse	547
Definition of Terms	548
Key Facts	548
Summary Points	548
References	549

51. The Plant *Salvia divinorum* (Lamiaceae)—Chemistry and Pharmacology

Adam W. Keasling and Jordan K. Zjawiony

Introduction	551
Chemistry	551
Pharmacology	554
Conclusion	557
Definition of Terms	557
Key Facts of the KOR	558
Summary Points	558
References	558

Section B

Molecular and Cellular Aspects

52. Pathophysiology of Ketamine Neurotoxicity: An Overview

Mustafa Aydin and Ugur Devenci

Introduction	563
Mechanism of Action	563

Chemical Characteristics	563
Ketamine Metabolism	563
Glutamate Receptors	563
Neuropathological Effects of the Ketamine	564
Excitotoxicity	566
Ketamine Neurotoxicity	567
Applications to Other Addictions and Substance Misuse	569
Definition of Terms	569
Key Facts	570
Summary Points	570
References	570

53. Neurometabolic Profiling of Ketamine: Changes in Neurotransmitter Pools

Antonio Napolitano and Martina Andellini

Introduction	573
Glutamate and Glutamine	573
Dopamine	574
Acetylcholine	576
GABA	576
Definition of Terms	578
Key Facts	578
Acknowledgment	578
References	578

54. Impact of Early Life Ketamine Exposure on the Developing Brain and Cognitive Sequelae: A Discussion of Apoptotic Neurodegeneration Mechanisms

Saurabh S. Kokane and Qing Lin

Introduction	581
Ketamine Pharmacology	581
Use of Ketamine in Pediatric Anesthesia	582
Side Effects and Limitations of Using Ketamine	583
Ketamine Neurotoxicity in the Developing Brain and the Resulting Cognitive Deficits	583
Molecular Mechanisms for Ketamine- Induced Neuroapoptosis	586
Applications to Other Addictions and Misuse	589
Definition of Terms	590
Key Facts of Ketamine's Use as an Anesthetic, Analgesic, and Antidepressant	590
Summary Points	590
References	591

55. Phencyclidine (Also Called Angel Dust or PCP) and the Firing Activity of Neurons

Eiichi Jodo

Effects of PCP on Electroencephalogram Activity	593
Effects of Systemic PCP on Neuronal Firing	594
Effects of Locally Applied PCP on Neuronal Firing	597
A Role of Tonic mPFC Activation in PCP-Induced Behavioral Abnormalities	597
Neural Mechanisms Mediating PCP-Induced Excitation of mPFC Neurons	597
Applications to Other Addictions and Substance Misuse	601
Definition of Terms	601
Key Facts of PCP	601
Summary Points	601
References	601

56. Phencyclidine (Angel Dust, PCP) and Fos Immunoreactivity

Hideko Yamamoto, Wakako Sawada, Etsuko Kamegaya, Yoko Hagino, Kazutaka Ikeda, Ichiro Sora, Masayoshi Mishina and Toshifumi Yamamoto

Introduction	604
Serotonergic and Cholinergic Innervations are Involved in PCP-Induced Hyperlocomotion	605
Lack of PCP-Induced Hyperlocomotion and Motor Impairment in GluN2D Knock Out Mice	606
Applications to Other Addictions and Substance Misuse	608
Definition of Terms	611
Key Facts	612
Summary Points	612
Acknowledgment	612
References	612

57. Effect of Phencyclidine on Neuregulin Expression, Cortical Interneurons, and Redox Dysregulation

Nataša Petronijević and Nevena V. Radonjić

Introduction	614
Effect of PCP on Neuregulin-1 Expression and Cortical Interneurons	614
PCP-Induced Redox Dysregulation in an Animal Model of Schizophrenia	616
PV Interneurons are Susceptible to the Harmful Effects of Free Radicals	619

Applications to Other Addictions and Substance Misuse	620
Definition of Terms	621
Key Facts	621
Summary Points	621
Acknowledgments	622
References	622

58. Involvement of Glutamate Transporters in Neuropathology of Phencyclidine Abuse

Akihiro Mouri, Hirotake Hida and Yukihiro Noda

Introduction	625
Behavioral Abnormalities and Expression Changes of Glutamate Transporter	626
Physiological Localization and Regulation of Glutamate Transporters, and the Efficacy of a Glutamate Transporter Inhibitor	629
Conclusion	631
Applications to Other Addiction/Dependence and Substance Misuse	631
Definition of Terms	632
Key Facts	633
Summary Points	633
References	633

Section C Structural and Functional Aspects

59. Antidepressant and Abuse Potential of Ketamine

H.W.W. Hasselmann

Introduction	639
Ketamine as an Antidepressant—Betting on the Wrong Horse?	639
Applications to Other Addictions and Substance Misuse	643
Conclusions	644
Definition of Terms	645
Key Facts	645
Summary Points	646
References	646

60. Ketamine and the Dissociatives: Comparisons with Schizophrenia

Joel Frohlich and John Darrell Van Horn

Introduction	649
Ketamine	649
Psychomimetic Effects	650
Glutamate and Dopamine Action	650
Other Neurotransmitter Action	652
Excitotoxicity	655

Electrophysiological Signatures	655	Definition of Terms	686
Conclusions, Limitations, and Future Directions	656	Key Facts About Subanesthetic Ketamine	686
Applications to Other Addictions and Substance Misuse	656	Summary Points	686
Definition of Terms	656	References	686
Key Facts of Schizophrenia	657		
Summary Points	657	64. The Acute and Chronic Effects of Ketamine as Revealed by Noninvasive Brain Imaging	
Acknowledgment	657	<i>Meng Li and Martin Walter</i>	
References	657	Introduction	689
61. Ketamine Mediates Psychosis through the Medial Septum, Hippocampus, and Nucleus Accumbens		Methods	690
<i>L. Stan Leung and Jingyi Ma</i>		Results	691
Introduction	661	Applications to Other Addictions and Substance Misuse	698
Ketamine in Animals	662	Conclusion	698
Conclusions	667	Definition of Terms	698
Applications to Other Addictions and Substance Misuse	668	Key Facts	699
Definition of Terms	668	Summary Points	699
Key Facts	668	References	699
Summary Points	668	65. Psychosis Induced by Phencyclidine (Also Called PCP or Angel Dust)	
References	669	<i>Tadahiro Katayama, Yoshiaki Suzuki and Eiichi Jodo</i>	
62. Recreational Use of Ketamine and Its Interaction with NMDA Receptors		Clinical Features	703
<i>Luís Félix, Luís Antunes, Sónia Campos, Carlos Venâncio and Ana Maria Coimbra</i>		Diagnosis	704
Introduction	672	Treatment	704
NMDA Receptor Overview	672	Course and Prognosis	704
Ketamine Characterization	674	Etiology, Pathology, and Pharmacology	704
Ketamine Pharmacology	674	Differences Between Acute and Chronic PCP Exposure	705
Ketamine and Human Abuse	676	Effects of PCP Exposure on Neurotransmission	705
Applications to Other Addictions and Substance Misuse	677	Implications for Schizophrenia	706
Conclusions	677	Applications to Other Addictions and Substance Misuse	710
Definition of Terms	677	Definition of Terms	710
Key Facts	678	Key Facts About Phencyclidine (PCP)-Induced Psychosis	710
Summary Points	678	Summary Points	710
References	678	References	711
63. Ketamine Usage at Subanesthetic Doses and Psychoactive Effects		66. Serotonin Projections, the Dorsal and Median Raphe Nuclei, and Phencyclidine (Also Called Angel Dust or PCP)	
<i>Daniel Flack and Elias Dakwar</i>		<i>Snezana Kusljic, Wendy Adams and Maarten van den Buuse</i>	
Introduction	681	Introduction: Phencyclidine	714
History and Pharmacology	681	Serotonin and Its Physiological Role	715
Subanesthetic Use	682	Central Serotonergic Neurons and Projections	715
Applications to Other Addictions and Substance Misuse	682		
Psychoactive Effects	683		
Conclusion	685		

Serotonin Receptors in the CNS	716	Key Facts About the History	
Animal Models Mimicking Illicit		of <i>Salvia divinorum</i>	736
Drug-Induced Behaviors	716	Summary Points	737
Effects of Raphe Lesions on Brain Serotonin		References	737
Concentrations and the Action of			
Phencyclidine	716	69. The Widely Available Hallucinogenic	
Localization of the Role of Brain Serotonin		Plant <i>Salvia divinorum</i> and Its Main	
Projections in the Hippocampus, Medial		Component, Salvinorin A	
Prefrontal Cortex, and Amygdala in		<i>Eduardo R. Butelman and Mary Jeanne Kreek</i>	
Phencyclidine-Induced Behaviors	718	Introduction	739
Conclusion	719	Applications to Other Addictions and	
Applications to Other Addictions and		Substance Misuse	742
Substance Misuse	719	Definition of Terms	743
Definition of Terms	719	Key Facts About the κ -Opioid Receptor	
Key Facts About Understanding the Role of		(KOP-r)/Dynorphin System	743
Serotonin in Psychosis Through the Study		Summary Points	743
of Phencyclidine Effects	720	Acknowledgments	744
Summary Points	720	References	744
References	720		
67. Phencyclidine (PCP)-Induced Deficits		Section D	
in Novel Object Recognition		Methods	
<i>Nichole M. Neugebauer, Lakshmi Rajagopal,</i>			
<i>Mei Huang and Herbert Y. Meltzer</i>		70. Enzyme Immunoassay for Salvinorin	
Introduction	723	A (a Main Component in <i>Salvia</i>	
PCP Models of Cognitive Impairment	724	<i>divinorum</i>)	
Applications to Other Addictions and		<i>Hiroyuki Tanaka, Madan Kumar Paudel, Osamu</i>	
Substance Misuse	728	<i>Shirota, Kaori Sasaki-Tabata, Setsuko Sekita and</i>	
Definition of Terms	728	<i>Satoshi Morimoto</i>	
Key Facts About Phencyclidine and		Introduction	749
Novel Object Recognition	729	Conclusion	753
Summary Points	729	Applications to Other Addictions and	
Disclosures/Acknowledgments	730	Substance Misuse	753
References	730	Definition of Terms	754
		Key Facts About Salvinorin A	754
68. Behavioral and Psychological Effects		Summary Points	754
of <i>Salvia divinorum</i>: A Focus on Self-		Acknowledgment	755
Reported Subjective Acute Behavioral		References	755
Effects and Laboratory Studies			
<i>Peter H. Addy</i>		Part IV	
Introduction	733	Hallucinogens	
Prevalence and Use Patterns for		Section A	
<i>Salvia divinorum</i>	733	General Aspects	
Self-Reported Subjective Effects of			
<i>Salvia divinorum</i>	734	71. Hallucinogenic Plants in the	
Observed Acute Behavioral Effects of		Mediterranean Countries	
<i>Salvia divinorum</i>	735	<i>Ioannis D. Passos and Maria Mironidou-Tzouveleki</i>	
Human Subjects Laboratory Studies with		<i>Phalaris aquatica</i>	761
Salvinorin A	735	Applications to Other Addictions	
Summary of Research	735	and Substance Misuse	762
Application to Other Addictions			
and Substance Misuse	736		
Definition of Terms	736		

Key Facts About <i>Phalaris aquatica</i>	763		
<i>Peganum harmala</i>	763		
Applications to Other Addictions and Substance Misuse	764		
Key Facts About <i>Peganum harmala</i> <i>Anadenanthera colubrina</i> and <i>Anadenanthera peregrina</i>	764		
Applications to Other Addictions and Substance Misuse	765		
Key Facts About <i>Anadenanthera colubrina</i> and <i>Anadenanthera peregrina</i>	765		
Plants Containing Atropine and Scopolamine	765		
Applications to Other Addictions and Substance Misuse	766		
Key Facts About Plants Containing Atropine and Scopolamine	766		
<i>Mandragora officinarum</i>	766		
<i>Atropa belladonna</i>	767		
Applications to Other Addictions and Substance Misuse	767		
<i>Hyoscyamus niger</i>	768		
<i>Datura stramonium</i>	768		
Definition of Terms	769		
Summary Points	769		
References	770		
Further Reading	772		
72. Use of LSD by Mental Health Professionals			
<i>Petr Winkler, Ingmar Gorman and Rita Kočárová</i>			
Introduction	773		
Self-Experiments with Mescaline in the Former Czechoslovakia	773		
LSD Research in the Former Czechoslovakia	773		
The Psychiatric Department of the General University Hospital in Prague	774		
Psychiatric Clinic in Sadská	776		
Psychiatric Research Institute in Prague	777		
Psychiatric Hospital in Kroměříž	778		
Reflections of Those Involved in LSD Self-Experimentation	779		
Renewed Hallucinogen Research at the National Institute of Mental Health	779		
Applications to Other Addictions and Substance Misuse	779		
Definition of Terms	779		
Key Facts	779		
Summary Points	780		
References	780		
73. Neurobiology of the Effects of Psilocybin in Relation to Its Potential Therapeutic Targets			
<i>Filip Tyls, Tomas Palenicek and Jiri Horacek</i>			
Introduction	782		
Neurobiology of Psilocybin's Action	784		
Therapeutic Targets	786		
New Insights	789		
Conclusions	790		
Definition of Terms	790		
Key Facts	791		
Summary Points	791		
Acknowledgment	791		
References	791		
74. A Profile of Those Who Use Hallucinogenic Mushrooms			
<i>Mitchell G. Spring, Rory D. Ostrow and Robert M. Hallock</i>			
Introduction	794		
Recreational Use	794		
Self-Medication	795		
Accidental Ingestion	796		
Summary/Discussion	797		
Applications to Other Addictions and Substance Misuse	797		
Definition of Terms	798		
Key Facts About Hallucinogenic Mushroom Use	798		
Summary Points	798		
References	798		
Section B Molecular and Cellular Aspects			
75. Molecular and Cellular Basis of Hallucinogen Action			
<i>James B. Hanks and Javier González-Maeso</i>			
Introduction	803		
Historical Point of View	803		
Chemical Structure	804		
Receptor Target	804		
Signaling Mechanisms	807		
Applications to Other Addictions and Substance Misuse	809		
Definition of Terms	810		
Key Facts of Hallucinogen Action	810		
Summary Points	810		
Acknowledgment	810		
References	810		

76. Hallucinogens: Circuits, Behavior, and Translational Models

James B. Hanks and Javier González-Maeso

Neuronal Circuits	813
Transcriptome Fingerprint as Hallucinogen Predictor	814
Behavior Models	816
Clinical Potential	817
New Hallucinogens and Their Potential Risk	818
Conclusions	818
Applications to Other Addictions and Substance Misuse	818
Definition of Terms	819
Key Facts of Hallucinogen Action	819
Summary Points	819
Acknowledgment	819
References	819

77. Hippocampal Neurogenesis: Effects of Psychedelic Drugs

Briony J. Catlow, Ahmad Jalloh and Juan Sanchez-Ramos

Discovery of Adult Neurogenesis	821
The Anatomy of Hippocampal Neurogenesis	821
Regulation of Neurogenesis in the DG	822
Serotonergic Innervation in the DG	824
Serotonin and Neurogenesis in the DG	824
Effects of Psychedelic Drugs on Hippocampal Neurogenesis	825
The Neurobiological Significance of Altered Hippocampal Neurogenesis Induced by Psychedelic Drugs	828
Summary	828
Applications to Other Addictions and Substance Misuse	829
Definition of Terms	829
Key Facts of Psychedelic Drugs and Hippocampal Neurogenesis	829
Summary Points	829
Acknowledgment	830
References	830

Section C Structural and Functional Aspects

78. Lysergic Acid Diethylamide and Mystical Experiences

Michael Lyvers

Introduction: Lysergic Acid Diethylamide in the Context of Other Psychedelic Agents	835
--	-----

Pharmacokinetic Aspects of LSD and Other Psychedelics	835
The Psychedelic Trip	836
Risks of Psychedelic Drug Use	836
Psychedelic Mystical Experiences	836
Mechanisms of LSD Action	837
Discovery of the Psychedelic Properties of LSD	838
LSD and a “Model Psychosis”	838
LSD as a Chemical Catalyst for Change	839
LSD, Mysticism, and Society	839
LSD and Mystical Experiences in the Twenty-first Century	840
Two Sides of LSD	842
Applications to Addictions and Substance Misuse	842
Definition of Terms	843
Key Facts	843
Summary Points	843
References	843
Further Reading	845

79. Tolerance to Lysergic Acid Diethylamide: Overview, Correlates, and Clinical Implications

T. Buchborn, G. Grecksch, D.C. Dieterich and V. Höllt

Introduction	846
Tolerance to LSD in Humans	846
Tolerance to LSD in Animals	849
Possible Mechanisms of Tolerance to LSD	852
Pathological and Therapeutic Implications of Repeated LSD Administration	855
Applications to Other Addictions and Substance Misuse	856
Definition of Terms	856
Key Facts of LSD	856
Summary Points	856
References	857

80. Schizophrenia Modeling Using Lysergic Acid Diethylamide

Charles D. Nichols

The History of Lysergic Acid Diethylamide, Serotonin, and Mental Disease	859
Human Models of Schizophrenia and Psychosis Using LSD	861
Early Animal Models	862
Current Rodent Models of Schizophrenia or Psychosis Using LSD	863
Summary	863
Summary Points	864
References	864

81. Psilocybin and Peak Experiences*Jennifer Lyke*

Introduction	866
Peak Experiences	866
Psychological Effects of Psilocybin	867
Experimental Research	867
Naturalistic Investigations	868
Long-Term Effects	871
Mechanisms	871
Applications to Other Hallucinogens and Substance Misuse	871
Conclusion	871
Definition of Terms	872
Key Facts of Psilocybin History	872
Summary Points	873
References	873

82. Psilocybin as an Inducer of Ego Death and Similar Experiences of Religious Provenance*Katarzyna Stebelska and Krzysztof Łabuz*

Introduction	875
The Connection between Schizophrenia-Like Psychosis and Religious Experiences	877
The Phenomenon of Ego Death	879
Possible Consequences of Ego Death Practicing for Social Life	879
Psilocybin-Induced Psychosis and Ego Death	880
Psilocybin-Induced Cognitive Deficits and Its Oneirogenic Activity	885
Concluding Remarks	886
Applications to Other Addictions and Substance Misuse	886
Definition of Terms	886
Key Facts of Scientific Interest on Psilocybin as an Adjuvant in Psychotherapy and Religious Practices	887
Summary Points	887
References	887

83. Psilocybin, Lysergic Acid Diethylamide, Mescaline, and Drug-Induced Synesthesia*Berit Brogaard and Dimitria Electra Gatzia*

Introduction	890
Drug-Induced Synesthetic Experiences and Other Hallucinogenic Effects	892
The Causal Role of Serotonin Receptors in Hallucinogenic Effects	894
The Mechanisms of Drug-Induced Synesthesia	897
Inhibition and Embodied Cognition	898

Conclusion	899
Applications to Other Addictions and Substance Misuse	900
Definition of Terms	900
Key Facts	900
Summary Points	901
References	901
Further Reading	905

**Section D
Methods****84. Assays for Detection of Fungal Hallucinogens Such as Psilocybin and Psilocin***Katarzyna Stebelska*

Introduction	909
Preparation of Fungal Samples	911
Preliminary Qualitative Analysis	911
Purification and Isolation	914
Preparation and Preliminary Purification of Body Fluid Samples	914
Derivatization of a Sample	917
Quantitative Analysis	917
Applications to Other Addictions and Substance Misuse	923
Definition of Terms	923
Key Facts About Psilocin/Psilocybin Isolation From Natural Sources and Findings Regarding Their Biosynthesis	924
Summary Points	924
References	924

**Part V
Anabolic Steroids, Inhalants and Solvents****Section A
General Aspects****85. Inhalant Use Disorders in the United States***Scott E. Bowen, Matthew O. Howard and Eric L. Garland*

Epidemiology of Inhalant Use in the United States	931
Acute Inhalant Intoxication	932
Inhalant Use Disorder	932
Natural History of Inhalant Use Disorder	934
Correlates of Inhalant Use	934
Pharmacology and Toxicology	935
Neuropathology and Other Organ Pathology	937
Screening and Assessment	939

Treatment	939
Prevention	939
Future Directions	939
Applications to Other Addictions and Substance Misuse	940
Definition of Terms	940
Key Facts of Inhalant Use in the United States	940
Summary Points	940
References	941

Section B

Molecular and Cellular Aspects

86. The Neuropathology of Adolescent Anabolic/Androgenic Steroid Abuse: Altered Development of the Reciprocal Hypothalamic Neural Circuit Controlling Aggressive Behavior

Richard H. Melloni Jr., Thomas R. Morrison and Lesley A. Ricci

Introduction	945
Applications to Other Addictions and Substance Misuse	954
Definition of Terms	954
Key Facts	955
Summary Points	955
Acknowledgment	955
References	955

87. Addiction to, Neurobiology of, and Genetics of Inhalants

Rasmon Kalayasiri and Michael Maes

Introduction	958
Mechanisms of Action	959
Genetic Markers for Inhalant Abuse	960
Applications to Other Addictions and Substance Misuse	961
Definition of Terms	961
Key Facts of Inhalant Addiction	962
Summary Points	962
References	962

88. The Effects of Abused Inhalants on Neurons Within the Addiction Neurocircuitry of the Brain

John J. Woodward and Jacob T. Beckley

Introduction	964
Definition and Classes of Abused Inhalants	964
Patterns of Abused Inhalant Use	965

Pathology Associated with Use of Abused Inhalants	965
Neurobehavioral Repercussions of Abused Inhalants	965
Molecular Targets of Abused Inhalants	965
Effects of Abused Inhalants on Neurons in the Addiction Neurocircuitry	967
Summary	974
Applications to Other Addictions and Substance Misuses	974
Definition of Terms	975
Key Facts	976
Summary Points	976
Acknowledgment	976
References	976

Section C

Structural and Functional Aspects

89. Anabolic Androgenic Steroids and Stroke

Carlos García Esperón, Elena López-Cancio M., Pablo García Bermejo and Antonio Dávalos E.

Stroke	981
Anabolic Androgenic Steroids	982
Stroke and AAS	983
Stroke Associated With Other Drug Addictions	984
Conclusions	987
Definition of Terms	988
Key Facts of Stroke	988
Summary Points	988
References	988

90. Testosterone and Striatal Dopaminergic Neurotoxicity

Dean E. Dluzen

Introduction	991
Testosterone: Neurotoxic or Neuroprotectant Agent?	991
Testosterone and NSDA Neurotoxicity: Background	991
Testosterone or Estrogen?	992
Testosterone: Modulation of Striatal Dopaminergic Function	992
Testosterone: Neurotoxicity Mechanisms as Revealed in Other Models	994
Testosterone: Intracellular versus Membrane Effects	994
Applications to Other Addictions and Substance Misuse	994
Definition of Terms	995
Key Facts	995
Summary Points	995
References	995

91. Acute and Long-Term Toxicity Caused by Addictive Inhalation of Nitrous Oxide and Impact on Neuropathology

Barbara Potocka-Banaś, Teresa Dembińska and Krzysztof Borowiak

Introduction	998
Pharmacokinetics of Nitrous Oxide	998
Receptor Mechanism of Action	999
Toxicity and Addiction to Nitrous Oxide	999
Death Due to Nitrous Oxide Acute Intoxication	1000
Impact of Hypoxemia on the Brain or Neurological Tissue	1000
Conclusions	1001
Applications to Other Addictions and Substance Misuse	1001
Definition of Terms	1001
Key Facts of Nitrous Oxide	1002
Summary Points	1002
References	1002

92. Toluene Abuse and White Matter Degeneration

Marc R. Del Bigio

Introduction	1004
Human White Matter Damage Documented by Imaging and Autopsy	1004
Is Toluene the Offending Compound?	1005
Animal Models of Toluene or Solvent Exposure and White Matter	1007
Pathogenesis of White Matter Damage Caused by Toluene	1007
Future Directions	1008
Applications to Other Addictions and Substance Misuse	1008
Definition of Terms	1008
Key Facts of Toluene Abuse	1008
Summary Points	1009
Acknowledgment	1009
References	1009

93. Chronic Toluene Exposure and the Hippocampal Structure in Adolescent and Adult Brains

Mzia Zhvania, Nadezhda Japaridze, Lela Chilachava, Lia Gelazonia and Nino Pochkhidze

Introduction	1012
Chronic Effect of Toluene Exposure Depends on the Age of the Organism Tested	1012

Chronic Toluene Exposure and Long-Term Outcomes	1013
Addiction and the Hippocampus	1013
Toluene Addiction and the Hippocampus	1013
Chronic Toluene Misuse and the Structure of the Hippocampus	1014
Different Vulnerabilities of Hippocampal Areas to Chronic Toluene Exposure	1015
Immediate and Persistent Effects of Chronic Toluene Exposure in Adolescents and Adults	1017
Applications to Other Addictions and Substance Misuse	1018
Definition of Terms	1018
Key Facts of Toluene Effects on the Hippocampal Structure	1018
Summary Points	1019
References	1019

Part VI International Aspects

94. Addictions in India

Debasish Basu, Abhishek Ghosh and Siddharth Sarkar

Introduction	1025
Traditional Substances of Use in India	1025
Changing Scenario in the Last Half Century	1026
Epidemiology of Substance Use Disorders in India	1027
Addiction Research in India	1027
Control Measures in India	1031
Conclusion	1032
Definition of Terms	1032
Key Facts	1032
Summary Points	1033
References	1033

95. Correlates and Gender Differentials of Opium Use Among Tribal Communities

Himanshu K. Chaturvedi, Ram C. Bajpai and Arvind Pandey

Introduction	1036
Traditional Beliefs of Tribes	1036
Household Survey on Substance Use	1037
Sociodemographic Distributions	1037
Opium Use and Gender Differentials	1037
Correlates of Opium Use	1037

Age of Initiation	1041	Definition of Terms	1073
Risk of Opium Use	1041	Key Facts	1073
Applications to Other Addictions and Substance Misuse	1043	Summary Points	1073
Definition of Terms	1043	References	1073
Key Facts	1043	Further Reading	1074
Summary Points	1043		
References	1043		
Further Reading	1044		
96. Genetic Aspects of Smoking Behavior in the Japanese Population		99. Inhalant Drug Use and Street Youth: Ethnographic Insights from Mexico City	
<i>Naomi Sato, Tomonori Sato and Haruhiko Sugimura</i>		<i>Roy Gigengack</i>	
Introduction	1046	Normalcy of Inhalants in Mexico City	1075
Nicotine-Metabolizing Enzymes	1047	Solvents and Glues	1076
Nicotinic Acetylcholine Receptors	1049	Inhalant Use and Youth	1078
Dopamine Pathway	1050	The “Taste” for “That Junk”	1079
Miscellaneous	1051	Vicio and Inhalant Fiends	1081
Genetic Polymorphisms and Polymorphisms in Smoking Behaviors	1051	Application to Other Addictions and Substance Use	1082
Applications to Other Addictions and Substance Misuse	1051	Definition of Terms	1082
Definition of Terms	1052	Key Facts About Inhalant Drug Use	1082
Key Facts of the Measurement of Nicotine Addiction	1052	Summary Points	1083
Summary Points	1052	References	1083
References	1052		
97. New Designer Drugs in Japan		100. Illegal Stimulants Use in Brazil: Epidemiological Aspects and Possible Reasons for High Consumption of Crack/Cocaine and Amphetamine- type Stimulants	
<i>Ruri Kikura-Hanajiri</i>		<i>Renata Rigacci Abdalla, Raul Caetano, Luciana Massaro, Sandro Mitsuhiro, Ilana Pinsky, Ronaldo Ramos Laranjeira and Clarice Sandi Madruga</i>	
Introduction	1055	Introduction	1085
The Prevalence of New Designer Drugs and Their Legal Status in Japan	1056	Results	1086
Conclusions	1062	Final Considerations	1088
Applications to Other Addictions and Substance Misuse	1062	Definition of Terms	1092
Definition of Terms	1062	Key Facts About Cocaine Use in Brazil	1092
Key Facts About the International Information Sharing Regarding New Psychoactive Substances	1062	Summary Points	1092
Summary Points	1063	References	1092
References	1063		
98. Addictions in South America		101. Addiction in Thailand	
<i>Martin Nizama-Valladolid</i>		<i>Rasmon Kalayasiri</i>	
Introduction	1066	Introduction	1094
Production	1066	Alcohol	1094
Trafficking and Distribution	1068	Tobacco	1095
Consumption	1068	Methamphetamine	1096
		Cannabis, Kratom, Inhalants, Opioids	1097
		Applications to Other Addictions and Substance Misuse	1098
		Definition of Terms	1098
		Summary Points	1098
		References	1098

102. Misuse of Benzodiazepines in France		BZD Diversion in France	1105
<i>Joëlle Micallef, Elisabeth Frauger and Maryse Lapeyre-Mestre</i>		Interventions and Strategies to Reduce Benzodiazepine Misuse in France	1108
Introduction	1101	Conclusion	1108
Overview of Benzodiazepine Use in Europe and in France	1101	Key Facts	1108
Pharmacoepidemiological View of Benzodiazepine Exposure in France	1102	Summary Points	1109
Characteristics of Benzodiazepine Use among Population Subgroups	1103	References	1109
		Index	1113

List of Contributors

- Renata Rigacci Abdalla** National Research Institute on Alcohol and Drugs (INPAD), Psychiatry Department – Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- Tomohiro Abekawa** Department of Psychiatry, Kotokukai, Aiko Hospital, Matsue, Japan
- Przemysław Adamczyk** Department of Community Psychiatry, Collegium Medicum of the Jagiellonian University, Kraków, Poland
- Wendy Adams** Department of Psychology, University of British Columbia, Vancouver, BC, Canada
- Peter H. Addy** Yale University School of Medicine, West Haven, CT, USA
- Yukio Ago** Laboratory of Medicinal Pharmacology, Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka, Japan
- María Álvaro-Bartolomé** Laboratory of Neuropharmacology, IUNICS/IdISPa, University of the Balearic Islands, Palma de Mallorca, Spain
- Martina Andellini** Medical Physics Department, Enterprise Risk Management, Bambino Gesù Children’s Hospital, Rome, Italy
- Matthew E. Andrzejewski** Department of Psychology, University of Wisconsin–Whitewater, Whitewater, WI, USA
- Gustavo A. Angarita** Department of Psychiatry, Clinical Neuroscience Research Unit, Connecticut Mental Health Center, Yale University School of Medicine, New Haven, CT, USA
- Mariana Angoa-Pérez** Research & Development Service, John D. Dingell VA Medical Center and Department of Psychiatry & Behavioral Neurosciences, Detroit, MI, USA
- John H. Anneken** Department of Psychiatry, Wayne State University, Detroit, MI, USA
- Luís Antunes** Centre for Research and Technology of Agro-Environment and Biological Sciences (CITAB), University of Trás-os-Montes and Alto Douro (UTAD), Vila Real, Portugal; Laboratory Animal Science (LAS), Institute for Research and Innovation in Health (I3S), University of Porto (UP), Porto, Portugal
- Yalda Hosseinzadeh Ardakani** Biopharmaceutics and Pharmacokinetics Division, Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
- Mustafa Aydin** Department of Paediatrics-Neonatology, Firat University School of Medicine, Elazig, Turkey
- Nima Badri** Student Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran
- Ram C. Bajpai** National Institute of Medical Statistics, Indian Council of Medical Research, New Delhi, India
- Daniel José Barbosa** UCIBIO/REQUIMTE (Rede de Química e Tecnologia), Toxicology Laboratory, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal; Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal; Cell Division Mechanisms Group, Institute for Molecular and Cell Biology – IBMC, Porto, Portugal
- Alfonso Barrós-Loscertales** Dpto. Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Castellon, Spain
- Debasish Basu** Department of Psychiatry, Postgraduate Institute of Medical Education & Research, Drug De-addiction & Treatment Centre, Chandigarh, India
- Benjamin Becker** Key Laboratory for NeuroInformation, Center for Information in BioMedicine, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, P. R. China
- Jacob T. Beckley** Department of Neurology, University of California – San Francisco, San Francisco, CA, USA
- Pablo García Bermejo** Stroke Medicine Department, Airedale General Hospital, West Yorkshire, UK
- Laís F. Berro** Department of Psychobiology, Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- Amanda L. Blaker** Department of Neurosciences, University of Toledo College of Medicine, Toledo, OH, USA
- Ede Bodoki** Department of Analytical Chemistry, Faculty of Pharmacy, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania

- Krzysztof Borowiak** Department of Clinical and Forensic Toxicology, Pomeranian Medical University, Szczecin, Poland
- Scott E. Bowen** Behavioral and Cognitive Neuroscience, Department of Psychology, Wayne State University, Detroit, MI, USA
- Patricia A. Broderick** Department of Physiology, Pharmacology & Neuroscience, The City University of New York School of Medicine, The Sophie Davis School of Biomedical Education, The City College of New York; Department of Biology, Neuroscience Division, The City University of New York Graduate School; Department of Neurology, New York University Langone Medical Center and Comprehensive Epilepsy Center, New York, NY, USA
- Berit Brogaard** Brogaard Lab for Multisensory Research, University of Miami, Coral Gables, FL, USA; Department of Philosophy, University of Oslo, Oslo, Norway
- Giovana Brolese** Center for Drug and Alcohol Research, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil
- T.M. Brunt** Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Utrecht, The Netherlands
- T. Buchborn** Institute of Pharmacology and Toxicology, Otto-von-Guericke University, Magdeburg, Germany
- Eduardo R. Butelman** Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, NY, USA
- Raul Caetano** University of Texas School of Public Health, Dallas, TX, USA
- Sónia Campos** Centre for Research and Technology of Agro-Environment and Biological Sciences (CITAB), University of Trás-os-Montes and Alto Douro (UTAD), Vila Real, Portugal; Laboratory Animal Science (LAS), Institute for Research and Innovation in Health (I3S), University of Porto (UP), Porto, Portugal
- Sofija V. Canavan** University of Chicago, Chicago, IL, USA
- João Paulo Capela** UCIBIO/REQUIMTE (Rede de Química e Tecnologia), Toxicology Laboratory, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal; FP-ENAS (Unidade de Investigação UFP em energia, Ambiente e Saúde), CEBIMED (Centro de Estudos em Biomedicina), Faculdade de Ciências da Saúde, Universidade Fernando Pessoa, Porto, Portugal
- Manolo Carta** Department of Biomedical Sciences, Section of Physiology, University of Cagliari, University Campus, Monserrato, Italy
- Félix Carvalho** UCIBIO/REQUIMTE (Rede de Química e Tecnologia), Toxicology Laboratory, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal
- Lucia Carvelli** Department of Pharmacology, Physiology and Therapeutics, University of North Dakota School of Medicine, Grand Forks, ND, USA
- Briony J. Catlow** University of South Florida, Tampa, FL, USA
- Young-Tae Chang** Department of Chemistry & MedChem Program of Life Sciences Institute, National University of Singapore, Singapore; Singapore Bioimaging Consortium, Agency for Science, Technology and Research (A*STAR), Singapore
- Himanshu K. Chaturvedi** National Institute of Medical Statistics, Indian Council of Medical Research, New Delhi, India
- Lela Chilachava** Institute of Chemical Biology, Ilia State University, Tbilisi, Georgia
- Aree Choodum** Faculty of Technology and Environment, Prince of Songkla University, Phuket, Thailand
- Shannon J. Clough** Department of Pharmacology & Toxicology, School of Medicine and Biomedical Sciences, University at Buffalo (SUNY), Buffalo, NY, USA
- Vanessa Coelho-Santos** Institute of Pharmacology and Experimental Therapeutics, Institute for Biomedical Imaging and Life Sciences (IBILI), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- Ana Maria Coimbra** Centre for Research and Technology of Agro-Environment and Biological Sciences (CITAB), University of Trás-os-Montes and Alto Douro (UTAD), Vila Real, Portugal
- Stuart A. Collins** Department of Neurosciences, University of Toledo College of Medicine, Toledo, OH, USA
- Bru Cormand** Departament de Genètica, Facultat de Biologia, Universitat de Barcelona, Barcelona, Catalonia, Spain; Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Catalonia, Spain; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Spain
- Albert Dahan** Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands
- Elias Dakwar** Division on Substance Abuse, Columbia College of Physicians and Surgeons, New York State Psychiatric Institute, New York, NY, USA
- Antonio Dávalos E.** Neurosciences Department, Germans Trias i Pujol Hospital, Universidad Autónoma Barcelona, Badalona (Barcelona), Spain

- Cor de Jong** Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA) and Radboud University Nijmegen, Nijmegen, The Netherlands
- Maria de Lourdes Bastos** UCIBIO/REQUIMTE (Rede de Química e Tecnologia), Toxicology Laboratory, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal
- Marc R. Del Bigio** Department of Pathology, Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada; Diagnostic Services Manitoba, Winnipeg, MB, Canada; Children's Hospital Research Institute of Manitoba, Winnipeg, MB, Canada
- Teresa Dembińska** Department of Clinical and Forensic Toxicology, Pomeranian Medical University, Szczecin, Poland
- Ugur Deveci** Department of Paediatrics, Firat University School of Medicine, Elazig, Turkey
- D.C. Dieterich** Institute of Pharmacology and Toxicology, Otto-von-Guericke University, Magdeburg, Germany
- Boukje Dijkstra** Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA) and Radboud University Nijmegen, Nijmegen, The Netherlands
- Dean E. Dluzen** Department of Life Sciences, John A. Logan College, Carterville, IL, USA
- Margarita L. Dubocovich** Department of Pharmacology & Toxicology, School of Medicine and Biomedical Sciences, University at Buffalo (SUNY), Buffalo, NY, USA
- Carlos García Esperón** Neurology Department, Cantonal Hospital Aarau, Aarau, Switzerland
- Chun-Kai Fang** Department of Psychiatry, Mackay Memorial Hospital, Taipei, Taiwan
- Vahid Farnia** Substance Abuse Prevention Research Center, Department of Psychiatry, Kermanshah University of Medical Sciences, Kermanshah, Iran
- Luís Félix** Centre for Research and Technology of Agro-Environment and Biological Sciences (CITAB), University of Trás-os-Montes and Alto Douro (UTAD), Vila Real, Portugal; Laboratory Animal Science (LAS), Institute for Research and Innovation in Health (I3S), University of Porto (UP), Porto, Portugal
- Noelia Fernández-Castillo** Departament de Genètica, Facultat de Biologia, Universitat de Barcelona, Barcelona, Catalonia, Spain; Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Catalonia, Spain; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Spain
- Daniel Flack** Division on Substance Abuse, Columbia College of Physicians and Surgeons, New York State Psychiatric Institute, New York, NY, USA
- Elisabeth Frauger** Center of Addictovigilance Paca Corse, Department of Clinical Pharmacology and Pharmacovigilance, APHM, Neurosciences Institut, UMRS CNR 7289, PIICI, Aix Marseille University, Marseille, France
- Joel Frohlich** Center for Autism Research and Treatment, University of California, Los Angeles, CA, USA
- Daniela F. Fukushiro** Department of Pharmacology, Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- Daniel A. García** IIBYT (CONICET-Universidad Nacional de Córdoba) Cátedra de Química Biológica, Depto. Química, Facultad de Ciencias Exactas, Físicas y Naturales, Universidad Nacional de Córdoba, Córdoba, Argentina
- M. Julia García-Fuster** Neurobiology of Drug Abuse Group, IUNICS/IdISPa, University of the Balearic Islands, Palma de Mallorca, Spain
- Jesús A. García-Sevilla** Laboratory of Neuropharmacology, IUNICS/IdISPa, University of the Balearic Islands, Palma de Mallorca, Spain
- Eric L. Garland** College of Social Work, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA
- Dimitria Electra Gatzia** Department of Philosophy, The University of Akron Wayne College, Orrville, OH, USA
- Lia Gelazonia** Laboratory of Neuron Ultrastructure and Nanostructure, Ivane Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia
- Abhishek Ghosh** Department of Psychiatry, Postgraduate Institute of Medical Education & Research, Drug De-addiction & Treatment Centre, Chandigarh, India
- Roy Gigengack** Department of Social and Cultural Anthropology, Vrije Universiteit; VU University Amsterdam, Amsterdam, The Netherlands
- Senobar Golshani** Substance Abuse Prevention Research Center, Department of Psychiatry, Kermanshah University of Medical Sciences, Kermanshah, Iran
- Joana Gonçalves** Institute for Biomedical Imaging and Life Science (IBILI), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- Javier González-Maeso** Virginia Commonwealth University School of Medicine, Richmond, VA, USA
- Ingmar Gorman** Department of Social Psychiatry, National Institute of Mental Health, Klecany, Czech Republic

- David K. Grandy** Department of Physiology & Pharmacology, School of Medicine, Oregon Health & Science University, Portland, OR, USA
- G. Grecksch** Institute of Pharmacology and Toxicology, Otto-von-Guericke University, Magdeburg, Germany
- Alissa M. Greer** School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
- Gary A. Gudelsky** James Winkle College of Pharmacy, University of Cincinnati, Cincinnati, OH, USA
- Casey Guillot** Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA
- Joshua M. Gulley** Department of Psychology and Neuroscience Program, University of Illinois, Urbana-Champaign, IL, USA
- Yoko Hagino** Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
- Robert M. Hallock** Neuroscience Program, Skidmore College, Saratoga Springs, NY, USA; Psychology Department, Purdue University Calumet, Hammond, IN, USA
- Emily R. Hankosky** Department of Psychology, University of Illinois, Urbana-Champaign, IL, USA
- James B. Hanks** Icahn School of Medicine at Mount Sinai, New York, NY, USA
- Carl Hart** Department of Psychology, Columbia University, New York, NY, USA; Department of Psychiatry, Columbia University, New York, NY, USA
- H.W.W. Hasselmann** Department of Psychiatry, Charité University Medicine Berlin, Berlin, Germany
- Hirotake Hida** Division of Clinical Sciences and Neuropsychopharmacology, Graduate School of Pharmacy, Meijo University, Nagoya, Japan
- Sarah E. Hodges** Yale University School of Medicine, New Haven, CT, USA
- Nicole Holder** Department of Psychology, University of Wisconsin–Whitewater, Whitewater, WI, USA
- André W. Hollais** Department of Pharmacology, Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- V. Höllt** Institute of Pharmacology and Toxicology, Otto-von-Guericke University, Magdeburg, Germany
- Jiri Horacek** National Institute of Mental Health (NIMH), Klecany, Czech Republic; 3rd Medical Faculty, Charles University in Prague, Prague, Czech Republic
- Matthew O. Howard** School of Social Work, University of North Carolina, Chapel Hill, NC, USA
- Fleur Margaret Howells** Department of Psychiatry and Mental Health, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
- Skye Hsin-Hsien Yeh** Brain Research Center and Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan
- Mei Huang** Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
- Anthony J. Hutchinson** Department of Pharmacology & Toxicology, School of Medicine and Biomedical Sciences, University at Buffalo (SUNY), Buffalo, NY, USA
- Jeng-Jong Hwang** Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan
- Kazutaka Ikeda** Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
- Jennifer E. Iudicello** The University of Houston, Houston, TX, USA
- Ahmad Jalloh** University of South Florida, Tampa, FL, USA
- Bardia Jamali** Biopharmaceutics and Pharmacokinetics Division, Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
- Nadezhda Japaridze** Laboratory of Neuron Ultrastructure and Nanostructure, Ivane Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia; New Vision University, Tbilisi, Georgia
- Eiichi Jodo** Department of Systems Neuroscience, Fukushima Medical University, School of Medicine, Fukushima, Japan
- Chantele Joordens** Center for Addictions Research of British Columbia, University of Victoria, Victoria, BC, Canada
- Rasmon Kalayasiri** Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
- Rama Kamal** Novadic-Kentron Addiction Center, Vught, The Netherlands
- Etsuko Kamegaya** Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
- Tadahiro Katayama** Department of Systems Neuroscience, Fukushima Medical University, School of Medicine, Fukushima, Japan
- Adam W. Keasling** Department of BioMolecular Sciences, School of Pharmacy, University of Mississippi, MS, USA
- Ruri Kikura-Hanajiri** Division of Pharmacognocny, Phytochemistry and Narcotics, National Institute of Health Sciences, Tokyo, Japan

- Matthew Kirkpatrick** Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA
- Béla Kiss** Department of Toxicology, Faculty of Pharmacy, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania
- Rita Kočárová** Department of Social Psychiatry, National Institute of Mental Health, Klecany, Czech Republic
- Saurabh S. Kokane** Department of Psychology, University of Texas at Arlington, Arlington, TX, USA
- Mary Jeanne Kreek** Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, NY, USA
- Peter R. Kufahl** Department of Psychology, Arizona State University, Tempe, AZ, USA
- Donald M. Kuhn** Research & Development Service, John D. Dingell VA Medical Center and Department of Psychiatry & Behavioral Neurosciences, Detroit, MI, USA
- Takeshi Kumazawa** Department of Legal Medicine, Showa University School of Medicine, Tokyo, Japan
- Snezana Kusljic** School of Health Sciences, The University of Melbourne, Melbourne, VIC, Australia
- Krzysztof Łabuz** Unit for Treatment of Addiction, Sahlgrenska University Hospital, Gothenburg, Sweden
- Maryse Lapeyre-Mestre** Département de Pharmacologie médicale et clinique, CHU de Toulouse, équipe de Pharmacoépidémiologie (INSERM 1027), Université de Toulouse, Toulouse, France
- Ronaldo Ramos Laranjeira** National Research Institute on Alcohol and Drugs (INPAD), Psychiatry Department – Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- Andrew J. Lawrence** Behavioural Neuroscience Division, Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia
- Byung Dae Lee** Department of Psychiatry, College of Medicine, Pusan National University & Hospital, Busan, South Korea
- Ricardo Alexandre Leitão** Institute of Pharmacology and Experimental Therapeutics, Institute for Biomedical Imaging and Life Sciences (IBILI), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- L. Stan Leung** Department of Physiology and Pharmacology, The University of Western Ontario, London, ON, Canada
- Chiang-Shan R. Li** Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; Department of Neuroscience, Yale University School of Medicine, New Haven, CT, USA; Interdepartment Neuroscience Program, Yale University, New Haven, CT, USA
- Meng Li** Department of Neurology, Otto v. Guericke University, Magdeburg, Saxony-Anhalt, Germany; Clinical Affective Neuroimaging Laboratory, Department for Behavioral Neurology, Leibniz Institute for Neurobiology, Otto v. Guericke University, Magdeburg, Saxony-Anhalt, Germany
- Qing Lin** Department of Psychology, College of Science, University of Texas at Arlington, Arlington, TX, USA
- Felicia Loghin** Department of Toxicology, Faculty of Pharmacy, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania
- Elena López-Cancio M.** Neurosciences Department, Germans Trias i Pujol Hospital, Universidad Autónoma Barcelona, Badalona (Barcelona), Spain
- Jennifer Lyke** School of Social and Behavioral Sciences, Stockton University, Galloway, NJ, USA
- Michael Lyvers** School of Psychology, Bond University, Gold Coast, QLD, Australia
- Scott Macdonald** Center for Addictions Research of British Columbia, University of Victoria, Victoria, BC, Canada
- Clarice Sandi Madruga** National Research Institute on Alcohol and Drugs (INPAD), Psychiatry Department – Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- Michael Maes** Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
- Timothy J. Maher** Department of Pharmaceutical Sciences, Massachusetts College of Pharmacy and Health Sciences (MCPHS) University, Boston MA, USA
- Jingyi Ma** Department of Physiology and Pharmacology, The University of Western Ontario, London, ON, Canada
- Chitra D. Mandyam** Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, La Jolla, CA, USA
- Claudia Mardones** Departamento de Análisis Instrumental, Facultad de Farmacia, Universidad de Concepción, Concepción, Chile
- Gina Martin** University of St Andrews, St Andrews, Fife, UK
- Luciana Massaro** National Research Institute on Alcohol and Drugs (INPAD), Psychiatry Department – Federal University of Sao Paulo, Sao Paulo, SP, Brazil

- Toshio Matsuda** Laboratory of Medicinal Pharmacology, Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka, Japan
- M.T.B. McMaster** Academic Medical Center, Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands; Amsterdam Institute for Addiction Research, Academic Medical Center, Amsterdam, The Netherlands
- Richard H. Melloni Jr.** Department of Psychology, Northeastern University, Boston, MA, USA
- Herbert Y. Meltzer** Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
- Joëlle Micallef** Center of Addictovigilance Paca Corse, Department of Clinical Pharmacology and Pharmacovigilance, APHM, Neurosciences Institut, UMRS CNR 7289, PIICI, Aix Marseille University, Marseille, France
- Maria Mironidou-Tzouveleki** A' Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
- Masayoshi Mishina** Ritsumeikan University Research Organization of Science and Technology, Kusatsu, Japan
- Sandro Mitsuhiro** National Research Institute on Alcohol and Drugs (INPAD), Psychiatry Department – Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- Christian Montag** Molecular Psychology, Institute of Psychology and Education, Ulm University, Ulm, Germany
- Elisabeth Moore** Graduate Program in Neuroscience, University of Minnesota, Minneapolis, MN, USA
- Erin E. Morgan** The University of Houston, Houston, TX, USA
- Peter T. Morgan** Department of Psychiatry, Clinical Neuroscience Research Unit, Connecticut Mental Health Center, Yale University School of Medicine, New Haven, CT, USA
- Satoshi Morimoto** Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan
- Thomas R. Morrison** Department of Psychology, Northeastern University, Boston, MA, USA
- Anna Moszczynska** Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA
- Akihiro Mouri** Division of Clinical Sciences and Neuropsychopharmacology, Faculty of Pharmacy, Meijo University, Nagoya, Japan
- Antonio Napolitano** Medical Physics Department, Enterprise Risk Management, Bambino Gesù Children's Hospital, Rome, Italy
- Nichole M. Neugebauer** Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
- Niamh NicDaeid** Centre for Anatomy and Human Identification, School of Science and Engineering, University of Dundee, Dundee, UK
- Charles D. Nichols** Department of Pharmacology and Experimental Therapeutics, LSU Health Sciences Center, New Orleans, LA, USA
- Martin Nizama-Valladolid** Department of Executive Management of Investigation, Teaching and Specialized Care for Addictions, National Institute of Mental Health "Honorio Delgado-Hideyo Noguchi", Lima, Peru
- Yukihiro Noda** Division of Clinical Sciences and Neuropsychopharmacology, Faculty of Pharmacy, Meijo University, Nagoya, Japan; Division of Clinical Sciences and Neuropsychopharmacology, Graduate School of Pharmacy, Meijo University, Nagoya, Japan
- Nicole A. Northrop** Department of Neurosciences, University of Toledo College of Medicine, Toledo, OH, USA
- M. Foster Olive** Department of Psychology, Arizona State University, Tempe, AZ, USA
- Rory D. Ostrow** Neuroscience Program, Skidmore College, Saratoga Springs, NY, USA
- Linda C.J. Oudejans** Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands
- Tomas Palenicek** National Institute of Mental Health (NIMH), Klecany, Czech Republic; 3rd Medical Faculty, Charles University in Prague, Prague, Czech Republic
- Arvind Pandey** National Institute of Medical Statistics, Indian Council of Medical Research, New Delhi, India
- Mariusz Papp** Behavioral Pharmacology Laboratory, Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland
- Ioannis D. Passos** A' Laboratory of Pharmacology, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
- Madan Kumar Paudel** Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan
- Maria A. Perillo** IIBYT (CONICET-Universidad Nacional de Córdoba) Cátedra de Química Biológica, Depto. Química, Facultad de Ciencias Exactas, Físicas y Naturales, Universidad Nacional de Córdoba, Córdoba, Argentina

- Christina J. Perry** Behavioural Neuroscience Division, Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia
- Nataša Petronijević** Institute of Clinical and Medical Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia
- Siripan Phattanasuddee** Department of Pharmacy Practice, Chulalongkorn University, Pathumwan, Bangkok, Thailand
- Iana Pinsky** National Research Institute on Alcohol and Drugs (INPAD), Psychiatry Department – Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- Nino Pochkhidze** Institute of Chemical Biology, Ilia State University, Tbilisi, Georgia
- Anca Pop** Department of Toxicology, Faculty of Pharmacy, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania
- Marianne Possa** Center for Drug and Alcohol Research, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil
- Barbara Potocka-Banaś** Department of Clinical and Forensic Toxicology, Pomeranian Medical University, Szczecin, Poland
- Boris B. Quednow** Experimental and Clinical Pharmacopsychology, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Zurich, Switzerland; Neuroscience Centre Zurich, University of Zurich and Swiss Federal Institute of Technology (ETH) Zurich, Zurich, Switzerland
- Nevena V. Radonjić** Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT, USA
- Lakshmi Rajagopal** Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
- Marta Ribasés** Psychiatric Genetics Unit, Hospital Universitari Vall d’Hebron, Barcelona, Catalonia, Spain; Institut de Recerca Vall d’Hebron (IRVH), Barcelona, Catalonia, Spain
- Lesley A. Ricci** Department of Psychology, Northeastern University, Boston, MA, USA
- Carola Vergara Rosales** Departamento de Análisis Instrumental, Facultad de Farmacia, Universidad de Concepción, Concepción, Chile
- Mohammad-Reza Rouini** Biopharmaceutics and Pharmacokinetics Division, Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
- Juan Sanchez-Ramos** University of South Florida, Tampa, FL, USA
- Renan Santos-Baldaia** Department of Pharmacology, Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- Siddharth Sarkar** Department of Psychiatry, All India Institute of Medical Sciences, National Drug Dependence Treatment Centre, Delhi, India
- Kaori Sasaki-Tabata** Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan
- Naomi Sato** Department of Clinical Nursing, Hamamatsu University School of Medicine, Shizuoka, Japan
- Tomonori Sato** Department of Shizuoka Physical Therapy, Faculty of Health Science, Tokoha University, Shizuoka, Japan
- Wakako Sawada** Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
- Silvia Bassani Schuch** Center for Drug and Alcohol Research, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil
- Setsuko Sekita** Laboratory of Pharmacognosy and Natural Products Chemistry, Kagawa School of Pharmaceutical Sciences, Tokushima University, Sanuki City, Kagawa, Japan
- Eduardo Alvear Serrano** Departamento de Laboratorio Servicio Médico Legal, Iquique, Región de Tarapacá, Chile
- Behjat Sheikholeslami** Faculty of Pharmacy, Lorestan University of Medical Sciences, Khorramabad, Iran
- Osamu Shiota** Laboratory of Pharmacognosy and Natural Products Chemistry, Kagawa School of Pharmaceutical Sciences, Tokushima University, Sanuki City, Kagawa, Japan
- Ana Paula Silva** Institute for Biomedical Imaging and Life Science (IBILI); Institute of Pharmacology and Experimental Therapeutics, Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- Nicola Simola** Department of Biomedical Sciences, Section of Neuropsychopharmacology, University of Cagliari, Cagliari, Italy
- Derek P. Simon** Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, NY, USA
- Ichiro Sora** Department of Psychiatry, Graduate School of Medicine, Kobe University, Kobe, Japan
- Anne Orgler Sordi** Center for Drug and Alcohol Research, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil
- Mitchell G. Spring** Neuroscience Program, Skidmore College, Saratoga Springs, NY, USA

- Katarzyna Stebelska** Department of Analytical and Ecological Chemistry, Faculty of Chemistry, Opole University, Opole, Poland
- Haruhiko Sugimura** Department of Tumor Pathology, Hamamatsu University School of Medicine, Shizuoka, Japan
- Yoshiaki Suzuki** Department of Systems Neuroscience, Fukushima Medical University, School of Medicine, Fukushima, Japan
- Kazuhiro Takuma** Laboratory of Medicinal Pharmacology, Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka, Japan
- Hiroyuki Tanaka** Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan
- Meshkat Torkamanian** Student Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran
- Pasarapa Towiwat** Department of Pharmacology and Physiology, Chulalongkorn University, Pathumwan, Bangkok, Thailand
- Anahí V. Turina** IIBYT (CONICET-Universidad Nacional de Córdoba) Cátedra de Química Biológica, Depto. Química, Facultad de Ciencias Exactas, Físicas y Naturales, Universidad Nacional de Córdoba, Córdoba, Argentina
- Filip Tyls** National Institute of Mental Health (NIMH), Klecany, Czech Republic; 3rd Medical Faculty, Charles University in Prague, Prague, Czech Republic
- J.G.C. van Amsterdam** Academic Medical Center, Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands; Amsterdam Institute for Addiction Research, Academic Medical Center, Amsterdam, The Netherlands
- W. van den Brink** Academic Medical Center, Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands; Amsterdam Institute for Addiction Research, Academic Medical Center, Amsterdam, The Netherlands
- Maarten van den Buuse** School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia
- John Darrell Van Horn** Keck School of Medicine, USC Mark and Mary Stevens Neuroimaging and Informatics Institute, University of Southern California, Los Angeles, CA, USA
- Martijn van Noorden** Leiden University Medical Center, Leiden, The Netherlands
- Monique van Velzen** Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands
- Carlos Venâncio** Centre for Research and Technology of Agro-Environment and Biological Sciences (CITAB), University of Trás-os-Montes and Alto Douro (UTAD), Vila Real, Portugal
- Dietrich von Baer** Departamento de Análisis Instrumental, Facultad de Farmacia, Universidad de Concepción, Concepción, Chile
- Lisia von Diemen** Center for Drug and Alcohol Research, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil
- Martin Walter** Department of Neurology, Otto v. Guericke University, Magdeburg, Saxony-Anhalt, Germany; Clinical Affective Neuroimaging Laboratory, Department for Behavioral Neurology, Leibniz Institute for Neurobiology, Otto v. Guericke University, Magdeburg, Saxony-Anhalt, Germany; Department of Psychiatry, Otto v. Guericke University, Magdeburg, Saxony-Anhalt, Germany; Department of Psychiatry, University of Tübingen, Baden-Württemberg, Germany
- Fang Wang** Department of Pharmacology, Shenyang Pharmaceutical University, Shenyang, China
- Erica Weber** The University of Houston, Houston, TX, USA
- Petr Winkler** Department of Social Psychiatry, National Institute of Mental Health, Klecany, Czech Republic
- Steven Paul Woods** The University of Houston, Houston, TX, USA
- John J. Woodward** Department of Neuroscience, Medical University of South Carolina, Charleston, SC, USA
- Chun-Fu Wu** Department of Pharmacology, Shenyang Pharmaceutical University, Shenyang, China
- Raphael Wuo-Silva** Department of Pharmacology, Federal University of Sao Paulo, Sao Paulo, SP, Brazil
- Wang Xu** Department of Chemistry & MedChem Program of Life Sciences Institute, National University of Singapore, Singapore; Singapore Peking Oxford Research Enterprise (SPORE), NUS Environmental Research Institute (NERI), Singapore
- Bryan K. Yamamoto** Department of Neurosciences, University of Toledo College of Medicine, Toledo, OH, USA
- Hideko Yamamoto** Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
- Toshifumi Yamamoto** Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan; Laboratory of Molecular Psychopharmacology, Graduate School of Nanosciences, Yokohama City University, Yokohama, Japan

Jing-Yu Yang Department of Pharmacology, Shenyang
Pharmaceutical University, Shenyang, China

Duanting Zhai Department of Chemistry & MedChem
Program of Life Sciences Institute, National University
of Singapore, Singapore

Mzia Zhvania Institute of Chemical Biology, Ilia State
University, Tbilisi, Georgia; Laboratory of Neuron

Ultrastructure and Nanostructure, Ivane Beritashvili
Center of Experimental Biomedicine, Tbilisi, Georgia

Jordan K. Zjawiony Department of BioMolecular
Sciences, School of Pharmacy, University of Mississippi,
MS, USA

This page intentionally left blank

Preface

The well-being of the individual is highly dependent on maintaining neurophysiological processes in a functional state but also on the ability to adapt to changes in the internal and external environments. However, adaptive changes may be pathological in some circumstances, with devastating consequences for the individual. Triggers for these neurological abnormalities are varied and may be due to life stages (e.g., aging), nutrition (e.g., nutrient deficiency or excess such as iodine and iron, respectively), trauma (e.g., metabolic or physical trauma, such as that due to hypoglycemia or blunt instruments), or drugs of addiction and substance misuse (e.g., nicotine, alcohol, caffeine, inhalants, and myriad others). The latter are common and preventable to some extent. For example, in the United States alone, there are an estimated 22 million illegal drug users. Of these, 60 million use tobacco, and 50 million misuse alcohol. Millions of individuals are also addicted to, or misuse, caffeine and prescription or over-the-counter medications.

As a consequence of addictions and substance misuse, adverse changes occur in affected tissues. These range from molecular and cellular perturbations to structural and functional abnormalities. It is possible that some of the science behind these changes may be applicable to other modes of neurophysiological imbalance. That is, lessons and features in one form of addiction and substance misuse may be transferable to another. Indeed, there are other forms of nonsubstance addictions such as gambling, gaming, and workaholism that may share common features, mechanisms, or outcomes. Understanding commonality provides a platform for studying specific addictions in more depth and allows one to speculate about new modes of understanding, causation, prevention, and treatment.

There is some difficulty in describing changes in human tissues, as this sort of information is rather limited in scope and analytical depth. Preclinical or nonclinical studies have advanced the detailed understanding of addictions and substance misuse considerably. These range from isolated structures, cells, and perfusions to invertebrates, rodents, and primates. It is thus essential to have both clinical and preclinical information within the same authoritative textual platform to advance our understanding of addictions and substance misuse.

Understanding neuropathology by itself can be somewhat problematic, especially in terms of addictions. This information needs to be placed within its wider context—from procurement of drugs, to altered behavior and psychosocial conditions. For some substances, there is very little molecular information, whereas for other drugs there is an abundance. The information on behavioral and psychosocial aspects is similarly divergent among the different addictions. Thus, any textual information on addictions and substance misuse/use requires a scientific continuum of information; with neurological features as a central core.

However, marshalling all the aforementioned information is somewhat difficult due to the wide array of material. To address this, the Editor has compiled *The Neuropathology of Drug Addictions and Substance Misuse*. It has three separate volumes:

Volume 1: Foundations of Understanding, Tobacco, Alcohol, Cannabinoids, and Opioids

Volume 2: Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants, and International Aspects

Volume 3: General Processes and Mechanisms, Prescription Medications, Caffeine and Areca, Polydrug Misuse, Emerging Addictions, and Nondrug Addictions

In compiling these volumes, we interspersed chapters to aid the holistic understanding of addictions and substance misuse. We present material not only on specific substances but also in major sections on the following:

Foundations for Understanding Substance Misuse and Their Effects

Emerging Addictions and Drugs of Abuse

International Aspects

Principles of Addictions, Overviews, Detailed Processes, and Mechanisms

Dual and Polydrug Abuse

Nondrug Addictions as Comparative Neuropathology

For Volume 1, the main parts are:

1—[1] Setting the Scene: Foundations for Understanding Substance Misuse and Their Effects

1—[2] Tobacco

- 1—[3] Alcohol
- 1—[4] Cannabinoids
- 1—[5] Opioids

For Volume 2, the main parts are:

- 2—[1] Stimulants
- 2—[2] Club Drugs
- 2—[3] Dissociative Drugs
- 2—[4] Hallucinogens
- 2—[5] Anabolic Steroids, Inhalants, and Solvents
- 2—[6] International Aspects

For Volume 3, the main Parts are:

- 3—[1] General Aspects: Principles of Addictions, Overviews, Detailed Processes, and Mechanisms
- 3—[2] Prescription Medications
- 3—[3] Caffeine and Areca (Betel Nut)
- 3—[4] Dual and Polydrug Abuse
- 3—[5] Emerging Addictions and Drugs of Abuse
- 3—[6] Nondrug Addictions as Comparative Neuropathology

Each part is split into different subsections:

General Aspects

Molecular and Cellular Aspects

Structural and Functional Aspects

Methods

It is tempting to focus exclusively on detection, prevention, and treatment. However, this would far extend the remit of the book. For example, the analysis of markers in alcoholism itself would merit a single book, as would public health prevention or treatment regimens. Instead, the book is focused on neuropathology with upstream and downstream causative scenarios, effects, and consequences. In the section **General Aspects**, basic information is provided to place the substance in context or to set the scientific scene. The section **Molecular and Cellular Aspects** provides greater detail. The section **Structural and Functional Aspects** is more broad-based and includes imaging, psychosocial, and behavioral aspects and other wider information. The section **Methods** contains selective techniques for screening and/or analysis. Of course, these are generalized divisions, and this is recognized by the Editor. Some articles in one section may also be well

sued to many other sections. Indeed, in a few cases we have located chapters within sections to complement other chapters; to impart a broader example of ideas, coverage, or concepts; to provide a more in-depth discourse that may be relevant to other drugs and their interactions; or to provide a greater understanding of substance and poly-substance misuse in general. However, the well-structured and professional index, provided by Elsevier, addresses issues in locating information, and so relevant material can be quickly found.

Each chapter has the following subheadings:

Applications to Other Addictions and Substance Misuse

Definition of Terms

Key Facts

Summary Points

These subheadings encompass unique features in the book that bridge the intellectual divide, so experts in one area of addiction may become more knowledgeable in another. These features will be very useful for the novice, student, or newly qualified health care professional. Others who wish to gain a broader understanding of addictions and substance misuse will also find these features of benefit.

The subheading **Application to Other Addictions and Substance Misuse** is intended to provide practical, speculative, or broader information. This is particularly useful when applied to those addictions in which there is a paucity of scientific material. For example, detailed molecular or functional information gathered from studying one addiction may be applicable to another.

Contributors are either international or national experts, leaders in the field, or trendsetters, and from respected institutions. Emerging fields of addictions and substance misuse are also incorporated in *Neuropathology of Drug Addictions and Substance Misuse*. This book is essential reading for addiction scientists, health care professionals, research scientists, molecular and cellular biochemists, and medical professionals including physicians and other practitioners, as well as those interested in health in general. It is also designed for professors, teachers, and lecturers; undergraduates, graduates, postgraduates, and libraries.

The Editor

MDMA (Ecstasy) and Gene Expression in the Brain: An Overview of Microarray and Candidate Gene Studies Assessing Transcriptional Changes in Rodents

Noelia Fernàndez-Castillo^{1,2,3}, Marta Ribasés^{4,5}, Bru Cormand^{1,2,3}

¹Departament de Genètica, Facultat de Biologia, Universitat de Barcelona, Barcelona, Catalonia, Spain; ²Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Catalonia, Spain; ³Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Spain; ⁴Psychiatric Genetics Unit, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain; ⁵Institut de Recerca Vall d'Hebron (IRVH), Barcelona, Catalonia, Spain

Abbreviations

BCL B cell leukemia/lymphoma
BDNF Brain-derived neurotrophic factor
CREB cAMP response element-binding protein
ERK Extracellular signal-regulated kinase
Fos FBJ osteosarcoma oncogene
GABA Gamma-aminobutyric acid
IEGs Induced early genes
KO Knockout
LTD Long-term depression
LTP Long-term potentiation
MAPK Mitogen-activated protein kinase
MDMA 3,4-Methylenedioxymethamphetamine (ecstasy)
NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells
NMDA N-Methyl-D-aspartate
SERT Serotonin transporter

INTRODUCTION

MDMA or 3,4-methylenedioxymethamphetamine (ecstasy) is a recreational drug of abuse that is widely used among adolescents and young adults. MDMA is a psychostimulant that induces euphoria, self-confidence, friendliness, empathy, and happiness in humans. MDMA also induces hyperthermia, which can eventually lead to toxicity and death. Chronic exposure to MDMA is related to hallucinations and to verbal, visual, and memory impairment, as well as psychiatric disorders such as psychosis and depression in humans (Baylen & Rosenberg, 2006). Much evidence supports the neurotoxic effects of MDMA in serotonergic neurons and the degeneration of neuronal fibers (dopaminergic neurons in mice) (Green, Mehan, Elliott, O'Shea, & Colado, 2003). MDMA has a high affinity for the serotonin transporter (SERT) and it increases serotonin release to the synaptic cleft. MDMA self-administration and its stimulant locomotor effect were abolished in mice lacking

Sert (−/−), showing the importance of SERT and the serotonergic system for the behavior and reward effects of MDMA (Trigo et al., 2007).

Compared to other drugs of abuse, such as cocaine, few studies have assessed the changes induced by MDMA in gene expression in brain. Most of them focus on specific candidate genes, selected on the basis of their function or their relation to MDMA targets or effects. This approach leads to bias and complicates the elaboration of hypotheses about the effect of the drug on gene expression and the possible mechanisms involved. In contrast, high-throughput approaches such as microarray studies allow examination of a wide range of genes without prior assumptions.

Here we review the main studies that have assessed changes in gene expression induced by MDMA intake by using high-throughput approaches, as well as some work that focuses on specific candidate genes. The studies analyze different brain regions involved in the behavioral and rewarding effects of MDMA (see Table 1 for details): (1) the brainstem (including raphe nuclei), which contains the serotonergic cell bodies that send axons to the cortex, limbic areas, and spinal cord; (2) the ventral striatum and the nucleus accumbens, which are the main areas involved in reward and are mostly mediated by dopaminergic neurons; (3) the amygdala, which is involved in mood; (4) the hippocampus, which is involved in memory; and (5) the frontal cortex, which regulates cognition, memory, and perception, exerts inhibitory control, and is involved in decision making.

Since acute effects of MDMA differ from those of chronic exposure, which causes serotonin or dopamine depletion in rodents, here we discuss separately the results obtained after passive acute and chronic administration, self-administration, and prenatal exposure to MDMA. Most of the studies reported here considered acute administration of the drug; a few examined chronic administration; and only one assessed self-administration or prenatal exposure (Table 1). We conclude our review by considering the outputs of all the studies to draw some hypotheses

TABLE 1 Microarray Studies of the Effects of MDMA on Gene Expression

Animal Model	Brain Region	MDMA Dose	Treatment	Time after Last Administration (Animals Killed)	Array Platform	Noteworthy Changes in Gene Expression	References
Rat	Frontal cortex	20 mg/kg intraperitoneally	Acute	0.5 h, 1 h, 2 h, 4 h, 8 h, 16 h, 1 day, 3 days, 7 days	Clontech Ratox12 microarray. 1176 genes	Cytokines, cytoskeleton, Egr, serotonin receptor 3	Thiriet et al. (2002)
Mouse	Substantia nigra (dopamine neurons)	47 mg/kg subcutaneously	Acute	8 h	15K Mouse Developmental cDNA Microarray. 15,264 genes	Metallothioneines	Xie et al. (2004)
Mouse	Dorsal striatum	9 mg/kg intraperitoneally	Acute	2 h	Affymetrix Mouse GeneChips, MGU74A. v2 and MG-U74B. v2. 24,000 genes	ERK signaling; transcription factors Fos and Egr; heat shock protein	Salzmann et al. (2006)
Rat	Frontal cortex, hippocampus, raphe	15 mg/kg intraperitoneally	Acute	3 weeks	Illumina RatRef-12 v1 beadarray expression chip. 15,983 genes	LTP, calcium, and ephrin signaling and neurotransmission	Petschner et al. (2013)
Mouse	Cerebral cortex, pons, cerebellum, midbrain, and hippocampus	1.25, 5, and 20 mg/kg orally	Chronic. Adolescent mice. Daily injection during 4 weeks.	11 days	AB Mouse Genome survey microarray. 32,381 genes	Cerebral cortex (20 mg/kg) MAPK, Wnt signaling, LTP, LTD	Eun et al. (2009)
Mouse	Frontal cortex, hippocampus, ventral striatum, dorsal raphe	0.125 mg/kg intravenously Total cumulative 19.7 mg/kg avg	Chronic. Active and passive (yoked self-administration). 3 h sessions during 11 days.	8 h	Affymetrix GeneChip Mouse Expression Set 430 array. 34,000 genes	Inflammatory and immune response LTP and MAPK signaling in active administration only in hippocampus and raphe	Fernández-Castillo et al. (2012)
Rat	Hippocampus	10 mg/kg intraperitoneally	Binge administration. 4 injections, each every 2 h.	18 h	Affymetrix GeneChip Rat Gene 1.0 ST array. 27,342 genes	Heat shock proteins and chaperones. Neuropeptide signaling. When previously chronically stressed: neuronal ensheathment	Weber et al. (2014)
Mouse	Cerebral cortex	20 mg/kg orally (mother)	Prenatal exposure (indirect). Daily for 4 weeks, from gestation day 6 to 3 weeks after birth.	8 weeks	AB Mouse Genome survey microarray. 32,381 genes	MAPK and Wnt signaling, axon guidance, cytoskeleton	Eun et al. (2010)

This table includes all microarray studies that have assessed MDMA-induced changes in gene expression, along with the main details of the experimental conditions, such as the animal used as a model, brain regions assessed, drug dose, and treatment. The main genes showing altered expression are highlighted.

regarding the mechanisms that underlie the response to MDMA exposure, from the first few hours to several days or weeks after administration.

ACUTE MDMA ADMINISTRATION

The main changes in gene expression observed after acute MDMA administration can be classified according to the functions that are affected (Table 2).

The first large-scale study that assessed the effect of MDMA on gene expression was performed in rats by Thiriet, Ladenheim, McCoy, and Cadet (2002); it assessed changes in gene expression in the frontal cortex of rats that had received a single injection of MDMA. A wide range of time points were considered after MDMA treatment. A total of 28 genes, divided into nine functional groups, showed differential expression over time: cytokines (*Mip1α* and *Mip3*), cell surface antigens (*Cd28* and *Iap*), BCL2 family proteins (*Bok*), cytoskeleton and matrix proteins (*Fib*, *Lama3*, *Nglyc*, and *Tubal1*), G-proteins (*Gγ9* and *Rab12*), intracellular kinase and the phosphatase network (*Cakβ*, *Mos*, *Ptp*, *Plcβ3* and *Rptpa*), metabolism (*Rps29*, *Gpx1*, *Hmox2*, *Hprt*, *Gapdh*, *Ldh-b*, and *Pub*), receptors (*5-ht3* and *Pgdr2*), and transcription (*Hox1.3*, *Egr-1* or *Ngfi-a* and *Ngfi-b*).

Those authors highlight changes in the expression of the gene for the serotonin receptor, *5-ht3*, which displays a 50% upregulation 4h after MDMA administration, then returns to its normal range and increases again after 3–7 days. The serotonergic system is the main MDMA target and is responsible for its behavioral effects. Other serotonin-related genes have also been assessed in different studies. Transcription of the serotonin receptor genes *5-ht1a* and *5-ht2c* was found to be diminished in the hippocampus after acute MDMA administration (Yau, Noble, & Seckl, 1997). A study performed by García-Osta, Del Rio, and Frechilla (2004) identified enhanced expression of *Tph*, encoding tryptophan hydroxylase, in the frontal cortex, and decreased expression in the hippocampus in rats after 2 days of acute MDMA administration. Also, expression of *Sert* increased in the raphe *pallidus* and *obscurus* 7 days after a single MDMA administration (Kovacs et al., 2007).

Peng and Simantov (2003) assessed gene expression changes in the frontal cortex and midbrain of mice 2h after acute MDMA treatment. Using Droplet Digital PCR (DD-PCR) they cloned 11 cDNA sequences that showed differential expression. Four of them corresponded to the genes coding for synaptotagmin 4 (*Syt4*), dystrophin (*Dmd*), septin (*Nedd5*), and GABA transporter (*Gat1*). The authors then focused on GABA transporters (GAT) and identified changes in gene expression in *Gat1* and *Gat4*, but not in *Gat2*. Both *Gat1* and *Gat4* displayed increased expression in the frontal cortex and midbrain, and expression of *Gat1* was sustained for 7 days after treatment. Furthermore, when *Gat1* expression was assessed in *Sert* knockout mice (–/–), which do not respond to MDMA, no significant induction of this GABA transporter was seen. They also studied the possible role of GAT in the toxic effects of MDMA and observed that after treatment with GAT inhibitors, a lethal MDMA dose decreased its toxicity significantly. The expression of the genes for the synaptic vesicle proteins SYT4 and SYT1 were further assessed by the group (Peng et al., 2002). It was observed that *Syt4* expression decreased, at RNA and protein levels, in the midbrain and

frontal cortex, whereas expression of *Syt1* increased in the midbrain, and that these changes in gene expression did not occur in the *Sert* KO mice.

Xie et al. (2004) performed a microarray study to identify genes involved in murine MDMA-induced toxicity in dopaminergic neurons. Mice were treated with a high dose of MDMA that produced significant dopaminergic depletion 1 week later. Substantia nigra was isolated 8 h after treatment to compare transcriptomic profiles, and 10 genes showing differential expression were identified: *Mt1* and *Mt2* (metallothioneins), *Ef1* and *Ef4* (translation factors), *Sgk*, *Cst3*, *Nd1*, *Mapk14*, *Hat1* and *Macf7*. *Mt1* and *Mt2* showed an upregulation peak 4h after MDMA administration and may protect dopaminergic neurons against MDMA-induced toxicity, since Mt-KO mice (*Mt1* (–/–) + *Mt2* (–/–)) showed larger dopamine deficits after repeated MDMA administration.

Salzmann, Marie-Claire, Le Guen, Roques, and Noble (2003) demonstrated that extracellular signal-regulated kinase (ERK) signaling plays an important role in MDMA-induced reward and behavioral responses in mice. Based on this, a subsequent study detected ERK activation by MDMA in dorsal striatum (Salzmann, Canestrelli, Noble, & Marie-Claire, 2006). Microarray technology was then used to study MDMA-induced changes in gene expression that were dependent on or independent of the ERK pathway. To that end, dorsal striatum profiles were analyzed in mice treated with an acute injection of MDMA with or without the ERK inhibitor SL327. Twenty-seven genes were identified, most upregulated, with differences in expression after acute MDMA administration; 16 of them were partially or totally inhibited by SL327 pretreatment. Nine of the ERK-dependent genes were validated (*Fos*, *Fosl2*, *Fosb*, *Egr1*, *Egr2*, *Rhoe*, *Dnajb5*, *Nts* and *Ttr*).

Among the genes altered by MDMA treatment that are affected by ERK inhibition, *Fos* and *Egr*-related transcripts (*Fos*, *Fosl2*, *Fosb*, *Egr1* and *Egr2*) deserve to be highlighted. Consistently, in the previous study, Salzmann et al. (2003) observed that 1h after acute MDMA administration, *c-fos* expression was greatly induced in the nucleus accumbens, caudate putamen, and hippocampus, and the expression of the *Egr1* and *Egr3* genes was increased in the caudate putamen. Other studies also identified *c-fos* induction in several brain regions after acute MDMA administration in mice and rats (Dragunow, Logan, & Laverty, 1991; Erdtmann-Vourliotis, Mayer, Riechert, & Holtt, 1999; Hashimoto, Tomitaka, Narita, Minabe, & Iyo, 1997; Stephenson, Hunt, Toppole, & McGregor, 1999). Increased expression of *Egr1* after acute MDMA exposure was also observed in the prefrontal cortex, striatum, and hippocampus of mice and also in the rat frontal cortex (Shirayama et al., 2000; Thiriet et al., 2002). *Fos* and *Egr* encode transcription factors and are MDMA-induced early genes (IEGs) that control late-response gene expression and may play an important role in the transition from short-term neuronal stimulation to long-lasting changes in neuronal function (O'Donovan, Tourtellotte, Millbrandt, & Baraban, 1999).

Another interesting result, which was explored further in another study by the same group (Marie-Claire, Benturquia, Lundqvist, Courtin, & Noble, 2008), is the increased expression of genes coding for several phosphatases in striatum following acute MDMA treatment. Upregulation of *Dusp14* depends on ERK, whereas *Dusp1* and *Dusp5* upregulation is ERK-independent. These three phosphatase-encoding genes are involved in the negative regulation of MAPK signaling; and regulation of protein

TABLE 2 Gene Expression Changes in Response to Acute MDMA Administration

Molecular Function	Representative Genes	Gene Symbol	References
Neurotransmission	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	<i>Slc6a3 (Sert)</i>	Garcia-Osta, Del Rio, and Frechilla (2004), Kovacs et al. (2007), Marie-Claire, Palminteri, et al. (2008), Nawata et al. (2010), Peng et al. (2002), Peng and Simantov (2003), Petschner et al. (2013), Thiriet et al. (2002), and Yau et al. (1997)
	5-Hydroxytryptamine (serotonin) receptor 3A	<i>5-ht3</i>	
	5-Hydroxytryptamine (serotonin) receptor 1A	<i>5-ht1a</i>	
	5-Hydroxytryptamine (serotonin) receptor 2C	<i>5-ht2c</i>	
	Tryptophan hydroxylase 1	<i>Tph1</i>	
	Tryptophan hydroxylase 2	<i>Tph2</i>	
	Solute carrier family 6 (neurotransmitter transporter, GABA), member 1	<i>Slc6a1 (Gat1)</i>	
	Solute carrier family 6 (neurotransmitter transporter, GABA), member 11	<i>Slc6a11 (Gat2)</i>	
	Gamma-aminobutyric acid (GABA) A receptor, subunit epsilon	<i>Gabre</i>	
	Glutamate receptor, ionotropic, AMPA 3	<i>Gria3</i>	
	Glutamate receptor, ionotropic, <i>N</i> -methyl D-aspartate 1	<i>Grin1</i>	
	Glutamate receptor, ionotropic, <i>N</i> -methyl D-aspartate 2a	<i>Grin2a</i>	
	Glutamate receptor, ionotropic, <i>N</i> -methyl D-aspartate 2b	<i>Grin2b</i>	
	Solute carrier family 1 (glial high affinity glutamate transporter), member 3	<i>Slc1a3</i>	
	Solute carrier family 1 (glial high affinity glutamate transporter), member 2	<i>Slc1a2</i>	
	Inflammatory and immune response and apoptosis	Cannabinoid receptor 1 (brain)	
Synaptotagmin IV		<i>Syt4</i>	
Neurotensin		<i>Nts</i>	
Chemokine (C–C motif) ligand 3		<i>Ccl3 (Mip-1a)</i>	
Chemokine (C–C motif) ligand 20		<i>Ccl20 (Mip-3)</i>	
Cd28 antigen		<i>Cd28</i>	
Protection from toxicity and hyperthermia	Cd47 molecule	<i>Cd47 (Iap)</i>	Adori et al. (2006), Escobedo et al. (2007), Stetler et al. (2010), Thiriet et al. (2002), Torres et al. (2010), and Xie et al. (2004)
	BCL2-related ovarian killer protein	<i>Bok</i>	
	Cannabinoid receptor 2 (macrophage)	<i>Cnr2 (Cb2)</i>	
	Metallothionein 1a	<i>Mt1</i>	
	Metallothionein 2	<i>Mt2</i>	
	Dnaj (Hsp40) homolog, subfamily B, member 5	<i>Dnajb5 (Hsc40)</i>	
Heat shock protein 1b	<i>Hspa1b (Hsp70)</i>		
Heat shock protein 2	<i>Hspb2 (Hsp27)</i>		
Heat shock protein 90, alpha (cytosolic), class A member 1	<i>Hsp90aa1 (Hspca)</i>		

TABLE 2 Gene Expression Changes in Response to Acute MDMA Administration—cont'd

Molecular Function	Representative Genes	Gene Symbol	References
	Heat shock factor 2	<i>Hsf2</i>	
	Glial fibrillary acidic protein	<i>Gfap</i>	
Neurotrophic factors	Brain derived neurotrophic factor	<i>Bdnf</i>	Adori et al. (2010) and Martinez-Turrillas et al. (2006)
Signal transduction	Eph receptor A4	<i>Epha4</i>	Marie-Claire, Benturquia, et al. (2008) and Petschner et al. (2013)
	Eph receptor A5	<i>Epha5</i>	
	Eph receptor A6	<i>Epha6</i>	
	Calcium/calmodulin-dependent protein kinase II inhibitor 1	<i>Camk2n1</i>	
	Calcium/calmodulin-dependent protein kinase II inhibitor 2	<i>Camk2n2</i>	
	Calcium/calmodulin-dependent protein kinase II gamma	<i>Camk2g</i>	
	Calcium/calmodulin-dependent protein kinase II beta	<i>Camk2b</i>	
	Dual specificity phosphatase 1	<i>Dusp1</i>	
	Dual specificity phosphatase 5	<i>Dusp5</i>	
	Dual specificity phosphatase 14	<i>Dusp14</i>	
Transcription factors	FBJ osteosarcoma oncogene	<i>Fos (c-fos)</i>	Dragunow et al. (1991), Erdtmann-Vourliotis et al. (1999), Hashimoto et al. (1997), Rodriguez-Alarcon, Canales, and Salvador (2007), Salzmann et al. (2003), Shirayama et al. (2000), Stephenson et al. (1999), and Thiriet et al. (2002)
	FBJ osteosarcoma oncogene B	<i>Fosb</i>	
	Fos-like antigen 2	<i>Fosl2</i>	
	Early growth response 1	<i>Egr1 (Ngfia)</i>	
	Early growth response 2	<i>Egr2</i>	
	Early growth response 1	<i>Egr3</i>	
	Nuclear receptor subfamily 4, group A, member1	<i>Nr4a1 (Ngfib)</i>	
Cytoskeleton	Rho family GTPase 3	<i>Rnd3</i>	Beveridge et al. (2004), Marie-Claire et al. (2007), and Thiriet et al. (2002)
	Rad and gem related GTP binding protein 2	<i>Rem2</i>	
	Tubulin, alpha 1A	<i>Tuba1a</i>	
	Activity regulated cytoskeletal-associated protein	<i>Arc</i>	

This table shows the main genes showing differences in gene expression after an acute MDMA administration. Genes are classified according to their molecular function, and references are specified for each functional category.

phosphorylation by phosphatase activity seems to be crucial for synaptic plasticity (Gurd, 1997).

Neurotensin (*Nts*), which modulates dopaminergic neurotransmission and is involved in several behavioral functions (reward, stress, and locomotion), was found to be upregulated in the microarray experiment (Salzmann, Canestrelli, Noble, & Marie-Claire, 2006) showing an overexpression peak 6h after acute MDMA treatment. Moreover, increased *Nts* expression was observed after chronic treatment, and treatment with

a neurotensin receptor antagonist modulated MDMA-conditioned place preference (CPP) and hyperlocomotor activity (Marie-Claire, Palminteri, et al., 2008). In rats, neurotensin also showed increased expression in the striatum 3h after acute treatment, as did two other neuropeptide genes: *Ppd* (preprodynorphin) and *Ppt* (preprotachykinin) (Adams, Hanson, & Keefe, 2005). *Ppd* was also found to be upregulated in rats in the prefrontal cortex, brainstem, and caudate, and down-regulated in the ventral tegmental area, 2h after acute MDMA

treatment (Di Benedetto, Bastias Candia Sdel, et al., 2011; Di Benedetto, D'Addario, Candeletti, & Romualdi, 2006).

The gene for the Rho GTPase involved in regulating actin cytoskeleton (*Rnd3*) showed overexpression both in the microarray and in a follow-up study in the hippocampus, striatum, and prefrontal cortex of mice treated acutely with MDMA (Marie-Claire, Salzmann, et al., 2007; Salzmann, Canestrelli, Noble, & Marie-Claire, 2006). Another gene involved in cytoskeleton reorganization (*Rem2*) also showed MDMA-induced expression in the microarray experiment.

The *Dnajb5* gene, encoding the heat shock protein HSC40, was upregulated, and another heat shock protein gene, *Hspa1b*, coding for HSP70, also showed increased expression in the frontal cortex 3 h and 7 days after acute MDMA administration in rat; this increase was dependent on the hyperthermic response (Escobedo, Peraile, Orio, Colado, & O'Shea, 2007). Elevated HSP27 was also identified in rat frontal cortex and hippocampus in astrocytes, as was GFAP in hippocampal astrocytes (Adori, Ando, Kovacs, & Bagdy, 2006). Heat-shock proteins can protect against damage caused by hyperthermia, free radicals, and ischemia (Stetler et al., 2010). Another study showed that MDMA induced significant hyperthermia, together with serotonin depletion and increased expression of the *Arc* gene in cortical regions, and the caudate putamen and hippocampus (Beveridge et al., 2004).

The last microarray study that evaluated acute MDMA effects on gene expression was performed by Petschner et al. (2013). Rats were treated with a single dose of MDMA and gene expression profiles of the hippocampus, frontal cortex, and dorsal raphe were assessed 3 weeks afterward. The authors identified a total of 615 genes differentially expressed in the MDMA-treated group: 481 of them in the hippocampus, 155 in the frontal cortex, and 14 in the dorsal raphe.

In the hippocampus, enrichment analysis identified clusters of genes involved in protein phosphorylation, dendrite and synapse development, synaptic plasticity, and transmembrane transport. Several genes encoding neurotransmitter receptors showed altered expression, such as the glutamate receptor genes *Gria3* and *Grin2a*, which were upregulated after acute MDMA administration, or the gene coding for the GABA-A receptor, epsilon subunit (*Gabre*), which was downregulated. The genes for several ephrin receptors (*Epha4*, *Epha5*, and *Epha6*), which modulate synapse formation and long-term potentiation (LTP) of glutamate, were found to be upregulated. Also, genes for members of the calcium signaling pathway (*Camk2n1*, *Camk2n2*, *Camk2g*, and *Camk2b*) and for calcium transporting ATPases (*Atp2b1* and *Atp2b3*) showed altered expression, as did genes encoding voltage-gated potassium transporters (*Kcn2* and *Kcnd2*). The cannabinoid receptor 1 gene (*Cnr1* or *Cb1*) was upregulated in this study and was also found to be increased in mouse hippocampus 7 days after repeated MDMA administration, whereas a CB1 receptor antagonist attenuated the cognitive deficits induced by MDMA (Nawata, Hiranita, & Yamamoto, 2010). Another study revealed increased expression of the CB2 receptor in the frontal cortex and hypothalamus in microglia after acute MDMA administration in rats, and showed that CB2 activation reduces neuroinflammatory response following MDMA administration (Torres et al., 2010).

In the frontal cortex, gene sets were related to protein synthesis and localization, transmembrane and nucleocytoplasmic transport, cell growth, chromatin maintenance, dendrite and

synapse development, and oxidoreductase activity. In this brain region, expression changes were also identified in genes related to calcium signaling (*Camk2g* and *Camk1g*), as well as an NMDA glutamate receptor (*Grin2b*) and a glutamate transporter (*Slc1a3*). A study performed in cortical cells in vitro identified an increase in the NMDA glutamate receptor NR1 (*Grin1*) and a decrease in the glutamate transporter EAAT2-1 (*Slc1a2* or *Glt1*) (Kindlundh-Hogberg et al., 2010).

Also, the genes coding for the heat shock protein HSPCA and the heat shock factor HSF2 were upregulated. In agreement with the results obtained by Thiriet et al. (2002), several growth factor gene sets showed upregulation, and others related to cytoskeletal transport showed downregulation.

In the dorsal raphe, only a few genes showed altered expression, among them the one encoding the glycine neurotransmitter transporter (*Slc6a5*).

If we consider all the above studies, which were performed following acute MDMA administration, it is possible to group the observed gene expression changes according to the distinct biological processes that they affect, which helps to elucidate the underlying molecular mechanisms (Table 2). The early events that occur after MDMA administration appear to be related to ERK activation and signal transmission (both ERK dependent and independent), which involve several kinases, phosphatases, and transcription factors (*Fos*- and *Egr*-related transcripts) and are an early response to MDMA. Afterward, some events involve changes in the regulation of neurotransmission: the serotonergic, glutamatergic, GABAergic, and cannabinoid systems. Also, MDMA-induced toxicity and hyperthermia activate inflammatory and immune responses, since some cytokines and cell surface antigens were found to be upregulated, as were some genes encoding proteins that protect against toxicity, such as heat shock proteins and metallothioneins. The later response to MDMA seems to involve synaptic plasticity, possibly mediated through calcium and ephrin signaling, and changes in the cytoskeleton and matrix proteins involved in neuroadaptation.

REPEATED AND CHRONIC MDMA ADMINISTRATION

The main gene expression changes that occur after repeated and chronic administration of MDMA are listed in Table 3.

Several studies that focus on repeated and chronic MDMA administration have assessed serotonergic, dopaminergic, and glutamatergic candidate genes. The serotonergic system is affected by long-term exposure to MDMA, which causes neurotoxicity due to serotonin depletion, leading to neurotransmitter dysregulation. After four binge administrations to rats (one per week), Kindlundh-Hogberg, Svenningsson, and Schioth (2006) observed increased expression of the *5-ht1b* gene in several brain regions (cortex, caudate putamen, and hypothalamus). In the same study, the *5-ht2a* and *5-ht2c* genes were also upregulated in the cortex; *5-ht2c* and *5-ht3* were upregulated in the hypothalamus; and *5-ht6* showed increased expression in the forebrain cortex and the amygdala. In another study, MDMA intake was found to diminish *5-ht1a* mRNA in the hippocampus and brainstem and to increase its expression in the frontal cortex (Aguirre, Frechilla, Garcia-Osta, Lasheras, & Del Rio, 1997). An in vitro study of rat cortical cells exposed to MDMA for 5 days identified a significant

TABLE 3 Gene Expression Changes in Response to Repeated and Chronic MDMA Administration

Molecular Function	Representative Genes	Gene Symbol	References
Neurotransmission	5-Hydroxytryptamine (serotonin) receptor 1A	<i>5-ht1a</i>	Aguirre et al. (1997), Biezonski and Meyer (2010), Bonkale and Austin (2008), Cuyas et al. (2014), Eun et al. (2009), Kindlundh-Hogberg et al. (2008), Kindlundh-Hogberg et al. (2010), and Kindlundh-Hogberg et al. (2006)
	5-Hydroxytryptamine (serotonin) receptor 1B	<i>5-ht1b</i>	
	5-Hydroxytryptamine (serotonin) receptor 2A	<i>5-ht2a</i>	
	5-Hydroxytryptamine (serotonin) receptor 2C	<i>5-ht2c</i>	
	5-Hydroxytryptamine (serotonin) receptor 3	<i>5-ht3</i>	
	5-hydroxytryptamine (serotonin) receptor 6	<i>5-ht6</i>	
	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	<i>Slc6a4 (Sert)</i>	
	Tryptophan hydroxylase 2	<i>Tph2</i>	
	Tyrosine hydroxylase	<i>Th</i>	
	Monoamine oxidase b	<i>Maob</i>	
	Solute carrier family 18 (vesicular monoamine), member 2	<i>Slc18a2 (Vmat2)</i>	
	Glutamate receptor ionotropic, AMPA1 (alpha1)	<i>Gria1</i>	
	Glutamate receptor ionotropic, AMPA2 (alpha2)	<i>Gria2</i>	
	Glutamate receptor metabotropic 1	<i>Grm1</i>	
	Glutamate receptor metabotropic 3	<i>Grm3</i>	
	Glutamate receptor metabotropic 5	<i>Grm5</i>	
	Glutamate receptor ionotropic, NMDA1 (zeta1)	<i>Grin1</i>	
	Glutamate receptor, ionotropic, NMDA2A (epsilon 1)	<i>Grin2a</i>	
	Glutamate receptor, ionotropic, NMDA2B (epsilon 2)	<i>Grin2b</i>	
	Solute carrier family 1 (glial high affinity glutamate transporter), member 3	<i>Slc1a3 (Eaat1)</i>	
	Solute carrier family 1 (glial high affinity glutamate transporter), member 2	<i>Slc1a2 (Eaat2-2)</i>	
Cholinergic receptor, muscarinic 3, cardiac	<i>Chrm3</i>		
Glycine receptor beta	<i>Glrb</i>		
Neuropeptide Y	<i>Npy</i>		
Solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 7	<i>Slc17a7</i>		
Inflammatory and immune response and apoptosis	Lipocalin 2	<i>Lcn2</i>	Fernandez-Castillo et al. (2012), Soleimani Asl et al. (2012), and Stumm et al. (1999)
	Cytotoxic T lymphocyte-associated protein 2 alpha	<i>Ctla2a</i>	
	Guanylate binding protein 2	<i>Gbp2</i>	
	Interferon gamma induced GTPase	<i>Igtp</i>	
	Interferon inducible GTPase 1	<i>ligp1</i>	
	Interferon inducible GTPase 2	<i>ligp2</i>	
	T cell specific GTPase 1	<i>Tgtp</i>	
B cell leukemia/lymphoma 2	B cell leukemia/lymphoma 2	<i>Bcl-2</i>	
	BCL2-associated X protein	<i>Bax</i>	
	BCL2-like 1	<i>Bcl2l1 (Bcl-x)</i>	

Continued

TABLE 3 Gene Expression Changes in Response to Repeated and Chronic MDMA Administration—cont'd

Molecular Function	Representative Genes	Gene Symbol	References
Protection from toxicity and hyperthermia	Heat shock protein 8	<i>Hspa8</i>	Weber et al. (2014)
	DnaJ (Hsp40) homolog, subfamily B, member 1	<i>Dnajb1 (Hsp40)</i>	
	Heat shock protein 1 (chaperonin)	<i>Hspd1</i>	
	Heat shock protein 90 alpha (cytosolic), class B member 1	<i>Hsp90ab1</i>	
	DnaJ (Hsp40) homolog, subfamily A, member 4	<i>Dnaja4</i>	
	DnaJ (Hsp40) homolog, subfamily B, member 11	<i>Dnajb11</i>	
	DnaJ (Hsp40) homolog, subfamily B, member 4	<i>Dnajb4</i>	
	DnaJ (Hsp40) homolog, subfamily A, member 2	<i>Dnaja2</i>	
	Serine (or cysteine) peptidase inhibitor, clade H, member 1	<i>SerpinH1 (Hsp47)</i>	
	Chaperonin containing Tcp1, subunit 5 (epsilon)	<i>Cct5</i>	
	Chaperonin containing Tcp1, subunit 6a (zeta)	<i>Cct6a</i>	
Neurotrophic factors	Brain derived neurotrophic factor	<i>Bdnf</i>	Eun et al. (2009) and Hatami et al. (2010)
	Neurotrophin 4	<i>Nt-4</i>	
Signal transduction	Purinergic receptor P2X, ligand-gated ion channel, 7	<i>P2rx7</i>	Eun et al. (2009)
	Vasoactive intestinal peptide receptor 1	<i>Vipr1</i>	
	Glycogen synthase kinase 3 beta	<i>Gsk3b</i>	
	Seven in absentia 1A	<i>Siah1</i>	
	Mitogen activated protein kinase kinase 7	<i>Map2k7</i>	
	Mitogen activated protein kinase kinase 2	<i>Map2k2</i>	
	Protein phosphatase 3, regulatory subunit B, alpha	<i>Ppp3r1</i>	
	Protein kinase C, beta	<i>Prkcb1</i>	
	DNA damage inducible transcript 3	<i>Ddit3</i>	
	TAO kinase 1	<i>Taok1</i>	

This table includes the main genes showing differences in gene expression after repeated or chronic MDMA administration. Genes are classified according to their molecular function, and references are specified for each functional category.

decrease in *5-ht3* expression and an increase in *5-ht1a* (Kindlundh-Hogberg et al., 2010). Seven days after a binge administration to rats, increased expression of the genes for tryptophan hydroxylase 2 (*Tph2*) and monoamine oxidase B (*Maob*), enzymes involved in serotonin synthesis and degradation, respectively, was observed in the hippocampus. The gene for tyrosine hydroxylase (*Th*), involved in dopamine synthesis, was downregulated in the striatum, and the serotonin transporter gene *Sert* and the vesicular monoamine transporter gene *Vmat2* showed diminished expression in the brainstem (Cuyas et al., 2014). Also, both in rat dorsal and medial raphe, *Tph2* expression was increased and *Sert* decreased 2 weeks after chronic and binge MDMA exposure, respectively (Biezonski & Meyer, 2010; Bonkale & Austin, 2008).

In rats, MDMA induces pronounced overexpression of the glutamate receptor and transporter genes *Gria2*, *Grm1*, *Grm5*, *Grin1*, *Grin2a*, *Grin2b*, *Eaat1*, and *Eaat2* in the cortex. The receptor genes *Gria2*, *Grin2a*, and *Grin2b* were increased in the caudate

putamen, and *Gria1*, *Gria3*, *Grm1*, and *Grm3* were upregulated in the hypothalamus, whereas *Gria1* was downregulated in the hippocampus (Kindlundh-Hogberg, Blomqvist, Malki, & Schioth, 2008). The expression of dopamine receptor genes was altered only in the hypothalamus (Kindlundh-Hogberg et al., 2006).

The first high-throughput study of gene expression changes was performed in adolescent mice several days after chronic MDMA exposure (Eun et al., 2009). The drug was administered daily at different doses for 4 weeks, and the highest dose showed the largest number of gene expression changes. The main changes were observed in the cerebral cortex, involving a total of 1028 genes, approximately half upregulated and half downregulated. These genes were involved mainly in signal transduction, transcription, protein modification, cell proliferation and differentiation, cell communication, transport, immunity, defense, apoptosis, and neurogenesis. The signaling pathways that were most altered were those of MAPK, Wnt, long-term potentiation (LTP),

long-term depression (LTD), and the neuroactive ligand–receptor interaction pathway. The set of differentially expressed genes included the following: *Npy*, *Chrm3*, *Grm1*, *P2rx7*, *Glr3*, and *Vipr1* (neuroactive ligand receptor interaction pathway); *Gsk3b* and *Siah1* (Wnt pathway); and *Bdnf*, *Map2k7*, *Map2k2*, *Ppp3r1*, *Prkcb1*, *Ddit3*, and *Taok1* (MAPK pathway). The MAPK signaling pathway is activated by growth factors, inflammation, stress, and cytokines and modulates several processes such as apoptosis, inflammation, differentiation, and cell growth (Bonni et al., 1999; Kaminska, 2005; Karin, 1998). This microarray experiment also showed upregulation of *Bdnf*, encoding a neurotrophic factor involved in the regulation of synaptic plasticity, survival, and the functioning of serotonergic neurons, together with many other processes. *Bdnf* is upregulated in response to brain damage and neuronal injury as a compensatory effect (Hicks, Martin, Zhang, & Serogy, 1999). In the parietal cortex of MDMA-treated rats, BDNF protein levels showed a robust peak increase 8 weeks after an acute administration (Adori et al., 2010). Another study (Martinez-Turrillas, Moyano, Del Rio, & Frechilla, 2006) focused on *Bdnf* expression and its relation with serotonin after MDMA administration in rats, since BDNF induces serotonin synthesis by enhancing *Tph* expression (Siuciak, Clark, Rind, Whittemore, & Russo, 1998). The study identified increased *Bdnf* expression in the frontal cortex 24–48 h after acute MDMA administration, and decreased expression in the hippocampus 2–7 days after drug intake. The investigators also studied the effect of MDMA on serotonin levels, and observed that upregulation of *Bdnf* in the frontal cortex seemed to play a role in the recovery of the levels of this neurotransmitter in this brain region, in contrast to the hippocampus, which showed no recovery after 7 days and which correlated with no increased expression of this gene. Augmented *Bdnf* expression correlated with higher levels of active CREB, enhanced expression of the *Tph* gene, and recovery of serotonin levels. *Tph* expression was increased after acute, repeated, and chronic MDMA administration in rats, as discussed above (Bonkale & Austin, 2008; Cuyas et al., 2014). Another neurotrophin gene, *Nt-4*, which encodes a molecule that acts through the same receptor as BDNF (TRKB), also showed increased expression in the brainstem, cerebellum, and cerebral hemisphere of rats after chronic MDMA administration for 5 days (Hatami, Hossainpour-Faizi, Azarfarin, & Azarfam, 2010). Neurotrophins might be involved both in protecting against MDMA-induced brain damage and in the neuronal remodeling that occurs after chronic drug use.

Another microarray study, performed by Fernandez-Castillo et al. (2012), evaluated changes in gene expression in the frontal cortex, ventral striatum, hippocampus, and dorsal raphe nucleus of mice after chronic MDMA administration (both passive and active) using a yoked control operant intravenous self-administration paradigm for 11 days. Gene expression was evaluated 8 h after the last administration. In the experiment, contingent mice were trained to self-administer MDMA. Each contingent mouse was connected to two other mice, one passively receiving an identical dose of MDMA and another receiving saline solution. This set-up allowed the identification of gene expression changes in active and passive administration. In what remains of this section, we focus on the effects of chronic MDMA administration on gene expression (shared between active and passive administration), and we leave for the next section the discussion on specific changes due to active self-administration. Changes in

gene expression due to direct effects of chronic MDMA, and displaying the same direction in both active and passive administration compared to the effects observed with saline, were identified in the ventral striatum (101 genes), frontal cortex (129), hippocampus (183), and dorsal raphe nucleus (16); most genes were upregulated in all brain regions. Similar enriched functions were observed in all brain regions, most of them involving immune and inflammatory responses, response to wounding, and stress. Similar enriched pathways were also identified, such as natural killer-mediated cytotoxicity, complement and coagulation cascades, and B cell receptor signaling. These functions and pathways emphasize the immunological and inflammatory nature of the response to chronic MDMA administration. The NF- κ B complex was a central node of gene networks for all four regions, and NF- κ B and RELA transcription factors (NF- κ B complex) were predicted to be responsible for the gene upregulation in all brain structures. Inflammatory and immunological responses might be modulated by NF- κ B, considering these results and previous studies showing that MDMA may induce NF- κ B activation (Montiel-Duarte, Ansorena, Lopez-Zabalza, Cenarruzabeitia, & Iraburu, 2004; Orio et al., 2010; Tiangco et al., 2005).

Some of the genes showing differential expression have immunological functions (*Lcn2*, *Ctla2a*, *Gbp2*, *Igtp*, *Iigp1*, *Iigp2*, and *Tgtp*), whereas others are involved in neurological processes (*Sgk1*, *Sgk3*, and *Slc17a7*). Most of the cited genes involved in immunological functions code for GTPases inducible by interferon- γ (INF- γ) and mediate interferon control of inflammatory and immunological responses. The lipocalin 2 gene (*Lcn2*), which is strongly overexpressed in all four brain regions, is induced after chronic and thermal stress and mediates astrocytosis under inflammatory conditions (Krishnan et al., 2007; Lee et al., 2009; Roudkenar et al., 2009).

Other studies showed that chronic MDMA exposure in rats induced neurotoxicity and apoptosis and altered the expression of some apoptotic genes. Long-term exposure to MDMA decreased cell viability in cultured rat cortical cells in a dose-dependent manner, and cell death was accompanied by differential expression of anti- and pro-apoptotic *Bcl-x* splice variants (Stumm et al., 1999). In the hippocampus of rats treated chronically, MDMA increased the expression of the pro-apoptotic gene *Bax* and decreased the expression of the anti-apoptotic gene *Bcl-2*, also in a dose-dependent manner (Soleimani Asl et al., 2012). As mentioned above, another gene of the *Bcl-2* family, *Bok*, was also altered after acute MDMA administration (Thiriet et al., 2002).

Another microarray study, by Weber, Johnson, Yamamoto, and Gudelsky (2014), assessed MDMA transcriptional changes in the hippocampus of rats exposed to chronic stress, which has been shown to increase MDMA-induced serotonergic toxicity. Rats under chronic stress were exposed to binge, repeated MDMA administration and killed 18 h after the last injection. The authors observed that MDMA alone (in nonstressed rats) induced changes in 1225 genes in the hippocampus, approximately half upregulated and half downregulated, involving functions such as calmodulin activity, protein kinase activity, protein folding, and neuropeptide signaling pathways. Regarding protein folding, a large number of genes for heat shock proteins and chaperones showed MDMA-induced overexpression (e.g., *Hspa8*, *Hsp40*, *Hspd1*, *Hsp90ab1*, *Cct5*, *Dnajb1*, *Dnaja4*, *Dnajb11*, *Dnajb4*, *Cct6a*, *SerpinH1*, or *Dnaja2*), in agreement with the results of other studies mentioned above (Adori et al., 2006; Escobedo et al., 2007; Salzmann et al., 2003).

MDMA combined with chronic stress induced altered expression of genes involved in responses to brain damage, especially neuronal ensheathment, categories in which changes were not observed when MDMA was administered to nonstressed rats. Also, in a context of chronic stress, MDMA altered the expression of genes involved in neurotransmission and sensory perception. Chronic stress seems to enhance neuronal damage caused by MDMA.

Taking into account all these studies of repeated and chronic administration, we can highlight some of the most notable gene expression changes induced by the drug, most of them related to its neurotoxic effects (Table 3). A few hours after the last administration, we observe pronounced immune and inflammatory responses that are probably induced by axonal serotonergic or dopaminergic depletion. These responses may be mediated by NF- κ B activation induced by MDMA. There is also increased neuronal death, accompanied by alterations in the expression of apoptotic genes. Brain damage can increase even more if the drug is consumed under stress conditions, altering neuronal ensheathment. Also, some heat shock proteins and chaperones are induced to provide protection against MDMA-induced toxicity. Neurotransmission-related genes, such as those encoding proteins related to serotonin and glutamate, are altered both as an adaptation to repeated exposure to the drug and also due to the depletion of the neurotransmitter. After a few days, several processes aid recovery from the damage, involving neuroadaptations and plasticity. These changes involve functions or molecules such as MAPK signaling and neurotrophins, Wnt signaling, LTP, LTD, and neuroactive ligand receptor signaling.

MDMA SELF-ADMINISTRATION

The only study of changes after MDMA self-administration that more closely mimics human MDMA intake was performed by Fernández-Castillo et al. (2012). As mentioned above, both chronic active self-administration (contingent) and passive administration induced changes in the expression genes involved in immune and inflammatory responses. That study also examined those genes involved in active self-administration learning processes compared to passive administration and saline solution. Positive genes were identified only in the hippocampus (645) and dorsal raphe nucleus (61), most of them downregulated and upregulated, respectively, in contingent mice. No significant differences in gene expression were identified in the frontal cortex or ventral striatum. Genes differentially expressed in the hippocampus were involved in neurological functions such as neurotransmission, regulation of synaptic plasticity, axonogenesis, learning, and memory. Also, several pathways were found to be altered both in the hippocampus and dorsal raphe nucleus, such as long-term potentiation (LTP), the MAPK signaling pathway, and the Wnt signaling pathway, in which most genes were downregulated in the hippocampus of contingent mice. All these pathways were found to be altered in adolescent mice after chronic MDMA administration (see above, Eun et al., 2009). Altered LTP genes included glutamate receptors (*Grin1*, *Grin2a*, and *Grin2b*) and phosphatases (*Ppp1cb* and *Ppp3ca*). Genes altered in the MAPK signaling pathway included *Ntrk2* (encoding a BDNF receptor), *Akt1*, and *Jund*.

Some of the genes involved in neurological processes that show differences in gene expression in the hippocampus were *Clpx2*, *Vamp2*, *Nrxn1*, *Nrx2*, *Amigo1*, *Bzrap1*, *Gprn1*, *Mapk8ip1*, *Nlgn2*, *Vgf*, *Madd*, and *Axin2*; and in the dorsal raphe

nucleus they were *Camk2a*, *Kalrn*, *Ddn*, and *Egr3*. These results suggest that both the hippocampus and dorsal raphe nucleus are involved in the motivation and learning processes associated with active MDMA seeking behavior, and that those processes are mediated through LTP, MAPK, and Wnt signaling pathways.

PRENATAL EXPOSURE TO MDMA

The effect of prenatal exposure to MDMA on gene expression has been investigated only by Eun et al. (2010). Unborn mice (male and female) were exposed indirectly to MDMA from gestation day 6 until 21 days after birth (during pregnancy and lactation), and cerebral cortex expression profiles were assessed 11 weeks later, using microarray technology. Prenatal exposure to MDMA induced differences in gene expression in 1784 genes in the female group and in 804 genes in the male group. Of these, 54 upregulated genes and 36 downregulated genes were common to both males and females. Enriched pathways shared by the male and female gene sets were the MAPK signaling pathway, Wnt signaling pathway, neuroactive ligand–receptor interaction pathway, calcium signaling pathway, and axon guidance and focal adhesion. This suggests that, although the genes showing differential expression are in general not the same between males and females, the processes involved in transcriptomic changes in both sexes are similar. Some of the genes differentially expressed under prenatal MDMA exposure were *Akt1*, *Atp1a2*, *H2afy*, *Ifit1*, *Rnase1*, and *Dctn1* in females and *Egr2*, *Arc*, *Rps2*, *Ppp3rl*, *Prkcb1*, and *Bcds3* in males. *Atp1a2*, *Dctn1*, and *Akt1* were highly upregulated (six- to sevenfold) in females.

Changes in gene expression that are present several days after prenatal MDMA exposure would involve neuroadaptive events, such as remodeling and synaptic plasticity. These events would help the brain to adapt to the effects caused by the drug during brain development.

MOLECULAR AND CELLULAR EVENTS TRIGGERED BY EXPOSURE TO MDMA

In the previous sections, we have seen how acute or chronic exposure to MDMA alters gene expression in the brain. This has been assessed using different experimental procedures and timings. Although MDMA-induced toxicity is much more pronounced after repeated and chronic administration, we have observed that common pathways are altered under both acute and chronic administration. The results obtained in each individual study provide only a static picture of the alterations in gene expression for a given time and experimental situation. By considering the data produced by all the above studies together, some conclusions can be drawn concerning the molecular events that take place upon MDMA administration, from the very first hours after exposure to the drug to several days or weeks afterward.

Early Response to MDMA Administration (Up to 2 Hours)

After MDMA administration, in which neurotransmission alterations such as increased serotonergic activity occur, the main downstream mechanism that is activated seems to be signal transmission

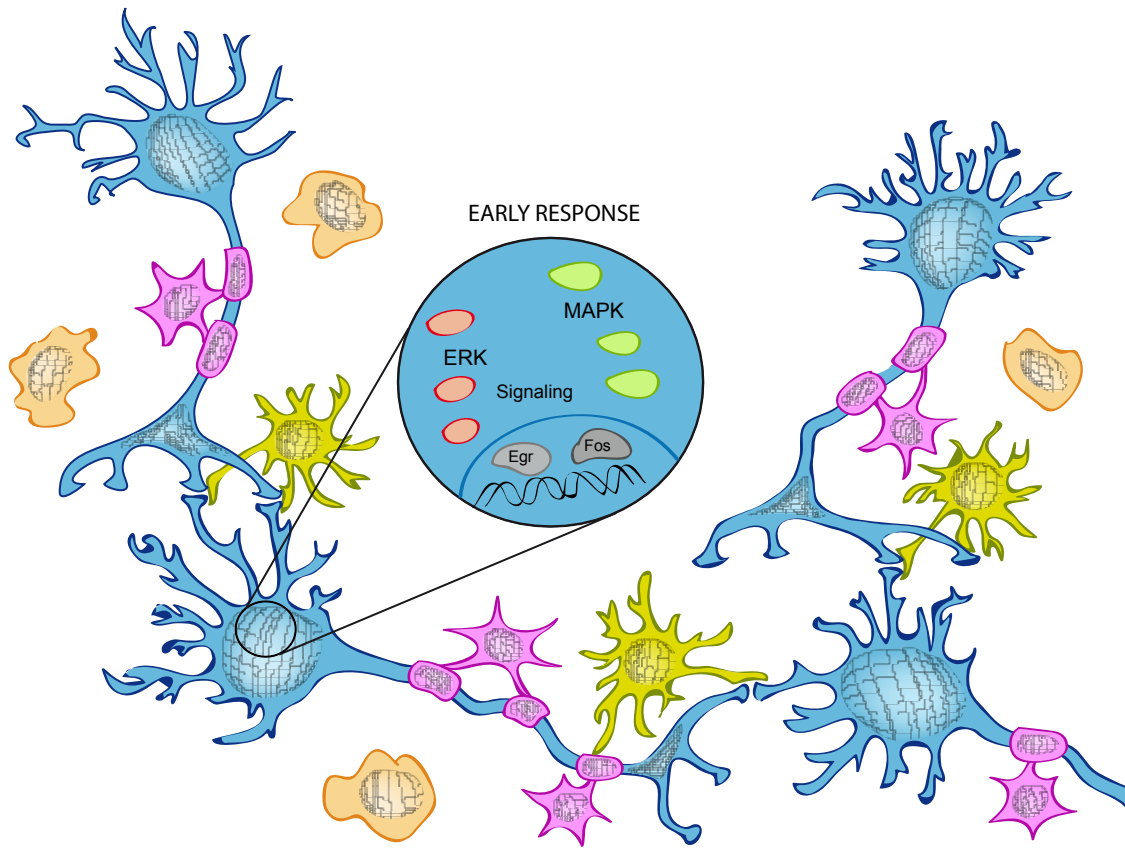


FIGURE 1 Early response to MDMA administration. Changes in gene expression up to 2 hours after drug administration affect mainly signal transmission (ERK and MAPK pathways) and *Fos*- and *Egr*s-related transcription factors, which produce the early response to MDMA. Neurons are indicated in blue, astrocytes in green, oligodendrocytes in purple, and microglia in orange.

(either through ERK activation or independently). MDMA induces changes in gene expression all along this signaling pathway, from kinases and phosphatases to transcription factors, such as FOS and EGR-related transcripts, forming the early response to the drug. [Figure 1](#) shows some neuronal and glial cells, and the signaling pathway and transcription factors that are altered in the postsynaptic neuron.

Later Response to MDMA Administration (More than 8 Hours)

After MDMA administration, several events take place. We observe expression changes in neurotransmission-related molecules, including receptors, transporters, neurotransmitter enzymes, and neuropeptides ([Figure 2](#)). These changes involve most neurotransmission systems, including the serotonergic, glutamatergic, GABAergic, dopaminergic, and cannabinoid systems, and they may be involved in compensating MDMA stimulation. Also, several signaling pathways are altered, such as MAPK, Wnt, and LTP, that are associated with learning and memory processes in active administration (such as memories related to the drug consumption involved in cue-induced craving). Finally, neurotoxicity-related processes occur, which are more intense at higher doses and with repeated administration. MDMA causes axonal depletion, and this induces an inflammatory and immune

response that tries to control brain damage. Glial cells probably help to remove cell debris and cellular content and act as a barrier to avoid toxicity in neighboring cells. Also, there is a cellular response that protects against MDMA-induced hyperthermia, which causes cell death.

Long-Term Response to MDMA Administration (Several Days to Weeks)

After brain damage, some neurotrophins help to recover synaptic function. Also, other synapses are potentiated ([Figure 3](#)). Several signaling pathways are required for neuroadaptations and synaptic plasticity, including the MAPK, Wnt, LTP, and LTD pathways, as well as cytoskeleton and matrix proteins.

Overall, only a few studies have assessed the effect of MDMA administration on gene expression. Microarray studies have some limitations, and better technologies are currently available, such as RNA-seq, which allows gene expression to be followed both quantitatively and qualitatively (i.e., by providing data about alternative splicing events). Future studies should consider different time points after the last drug administration; self-administration paradigms in rodents need to be explored further, as they mimic human MDMA use more closely. Also, studies of post mortem human brains should be performed.

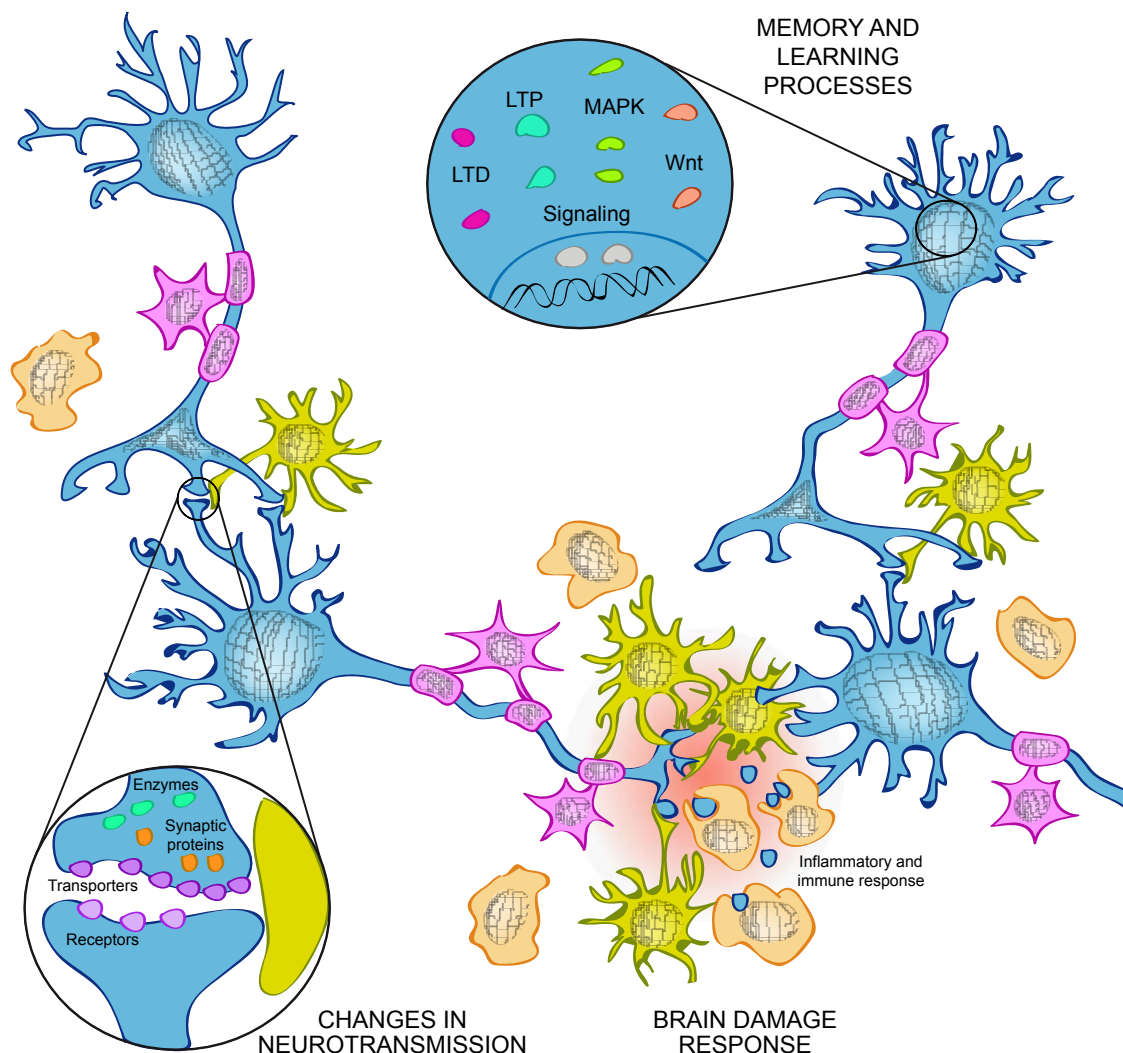


FIGURE 2 Late response to MDMA administration. Changes in gene expression more than 8 hours after drug administration affect different mechanisms. As a compensatory mechanism, several changes in genes related to neurotransmission occur, including those that encode synaptic proteins and neurotransmitter transporters, receptors, and enzymes. Gene expression changes in signaling pathways such as LTP, LTD, MAPK, and Wnt are involved in memory and learning processes in active self-administration. Also, due to toxicity and axonal depletion caused by MDMA, there are expression changes in genes involved in inflammatory and immune responses, in which astrocytes and microglia play an important role.

In summary, MDMA causes numerous alterations in gene expression, the most notable ones indicating induced toxicity in the brain and neuroadaptive processes that are activated to promote recovery from brain damage. These molecular and cellular alterations may have an impact on brain function, as several studies report cognitive impairments in ecstasy users.

APPLICATION TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

MDMA is an amphetamine derivative. Amphetamines and methamphetamines are, like MDMA, directly neurotoxic; and expression changes caused by these drugs of abuse seem to involve the same mechanisms as those involved in the effects of MDMA on brain (Yuferov, Nielsen, Butelman, & Kreek, 2005). Amphetamines alter the expression of some of the same genes altered after MDMA administration, such as *Ngfi-a*, *Ngfib*, *Arc*, and *Sgk*.

Methamphetamine-induced gene expression changes detected a few hours after drug intake involve transcription factors such as *Fos* and *Jun*, whereas genes related to apoptosis, inflammation, and neuroprotection become important only after several hours; similar to the expression changes induced by MDMA. Methamphetamine also activates microglia and increases *Bdnf* expression.

DEFINITION OF TERMS

Binge administration Administration of multiple doses within 24 h or less.

Expression microarray Matrix containing DNA fragments used as targets to hybridize a sample that allows the expression of thousands of genes to be tested.

Gene expression Process in which the information encoded in a gene is used to synthesize a gene product, which in most cases is, ultimately, a protein. When a gene is upregulated, its expression is

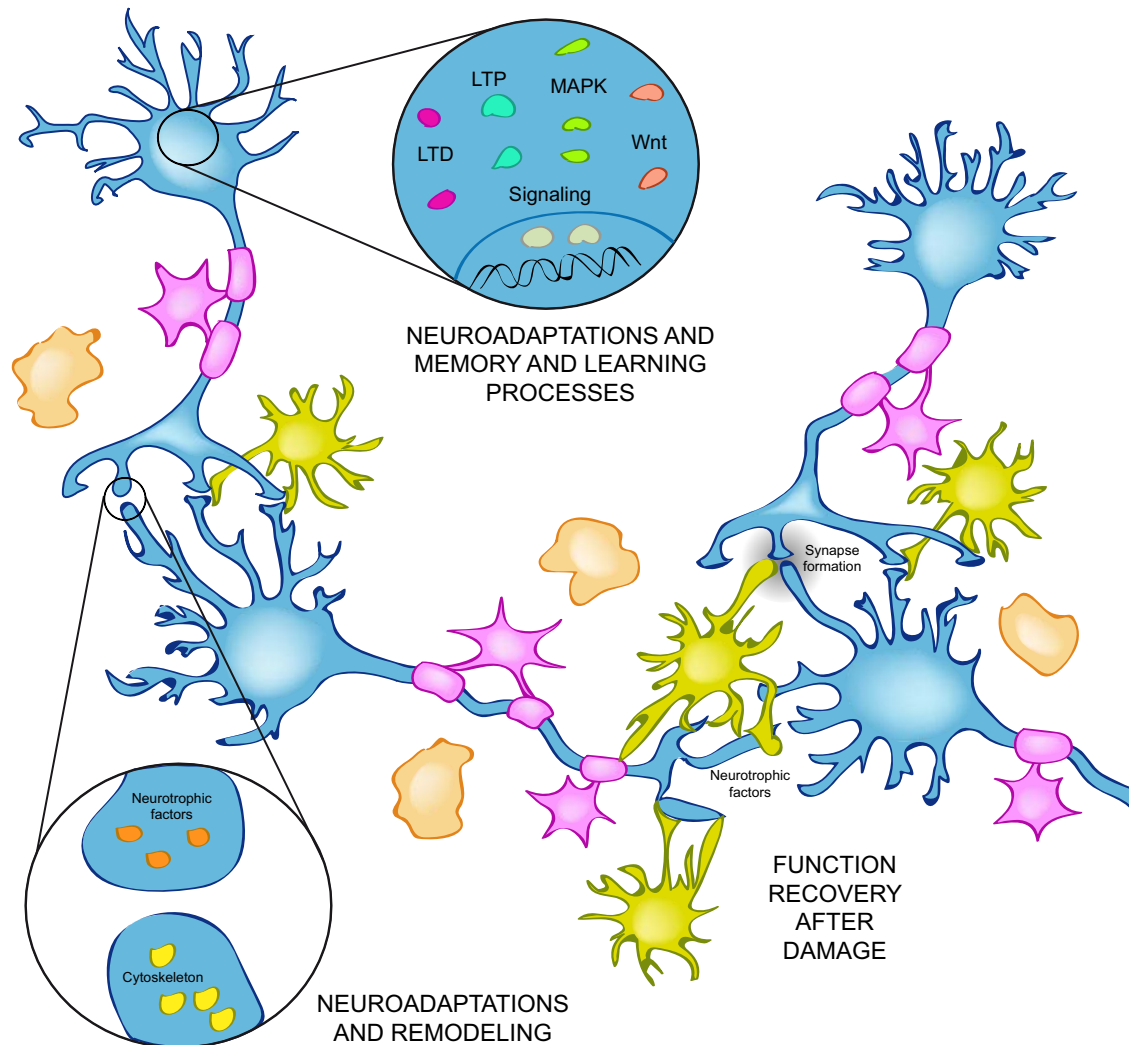


FIGURE 3 Long-term response to MDMA administration. Changes in gene expression days to weeks after drug administration affect mainly synapse formation, neuroadaptations, remodeling, and function recovery after damage. The underlying genes encode neurotrophic factors and proteins related to signaling pathways (LTP, LTD, MAPK, and Wnt) or the cytoskeleton.

increased, whereas when it is downregulated, its expression is decreased.

Long-term potentiation or depression Long-lasting potentiation or reduction, respectively, of the efficacy of the synapses between two neurons. They are considered the main mechanisms underlying learning and memory.

Neurotransmission Process of communication between neurons in which neurotransmitters are released by a presynaptic neuron and bind receptor molecules in one or more postsynaptic neurons.

Neurotrophic factor Growth factors involved in survival, growth, differentiation, and maintenance of neurons.

Signal transduction or signaling pathway Biochemical chain of events inside the cell triggered by an extracellular molecule that activates a receptor. The activation results in a response such as alteration of gene expression, cell shape, cell cycle, or metabolism.

Synaptic plasticity Changes in synapses resulting from increases or decreases in their activity: for instance, changes in receptor or transporter densities or in the amount of neurotransmitter released.

KEY FACTS

Key Facts about Drugs of Abuse

- All drugs of abuse converge on the activation of the reward system of the brain, causing pleasure, reward, and reinforcement.
- Drugs of abuse induce neuronal adaptations in the brain that can become stable over time.

Key Facts about Neurotransmission

- Neurons connect to each other through the release and capture of chemical compounds called neurotransmitters.
- Drugs of abuse alter the way that neurons communicate.

Key Facts about Gene Expression

- Drugs of abuse induce changes in gene expression in the brain.
- Expression of all genes in the genome can be easily monitored using microarrays.

SUMMARY POINTS

- This chapter focuses on the effects of MDMA on gene expression in the brain.
- No human studies are available yet, but animal models using different paradigms and conditions help to elucidate the molecular and cellular events that occur upon MDMA administration.
- Acute MDMA effects on gene expression differ from those caused by chronic exposure, in which neuronal depletion and cytotoxic effects are enhanced.
- During the first few hours after MDMA intake, the changes in gene expression involve signal transmission, which activates transcription factors that trigger an early response.
- Several hours after these initial molecular events, many neurotransmission-related genes show altered expression.
- At this point, genes related to the inflammation and immune responses are upregulated due to the cytotoxic effect of MDMA.
- Changes in the expression of specific genes occur as a response to MDMA-induced hyperthermia.
- Days after MDMA intake, the expression of genes involved in neuroadaptation and synaptic plasticity is altered to promote recovery from brain damage and adaptation of neuronal circuits.
- Therefore, MDMA causes brain damage and toxicity that can lead to cognitive impairments.

REFERENCES

- Adams, D. H., Hanson, G. R., & Keefe, K. A. (2005). 3,4-Methylenedioxy-methamphetamine increases neuropeptide messenger RNA expression in rat striatum. *Brain Research, Molecular Brain Research*, 133(1), 131–142.
- Adori, C., Ando, R. D., Ferrington, L., Szekeres, M., Vas, S., & Kelly, P. A. (2010). Elevated BDNF protein level in cortex but not in hippocampus of MDMA-treated DARK Agouti rats: a potential link to the long-term recovery of serotonergic axons. *Neuroscience Letters*, 478(2), 56–60.
- Adori, C., Ando, R. D., Kovacs, G. G., & Bagdy, G. (2006). Damage of serotonergic axons and immunolocalization of Hsp27, Hsp72, and Hsp90 molecular chaperones after a single dose of MDMA administration in Dark Agouti rat: temporal, spatial, and cellular patterns. *The Journal of Comparative Neurology*, 497(2), 251–269.
- Aguirre, N., Frechilla, D., Garcia-Osta, A., Lasheras, B., & Del Rio, J. (1997). Differential regulation by methylenedioxyamphetamine of 5-hydroxytryptamine_{1A} receptor density and mRNA expression in rat hippocampus, frontal cortex, and brainstem: the role of corticosteroids. *Journal of Neurochemistry*, 68(3), 1099–1105.
- Baylen, C. A., & Rosenberg, H. (2006). A review of the acute subjective effects of MDMA/ecstasy. *Addiction*, 101(7), 933–947.
- Beveridge, T. J., Mechan, A. O., Sprakes, M., Pei, Q., Zetterstrom, T. S., & Green, A. R. (2004). Effect of 5-HT depletion by MDMA on hyperthermia and Arc mRNA induction in rat brain. *Psychopharmacology*, 173(3–4), 346–352.
- Biezonski, D. K., & Meyer, J. S. (2010). Effects of 3,4-methylenedioxyamphetamine (MDMA) on serotonin transporter and vesicular monoamine transporter 2 protein and gene expression in rats: implications for MDMA neurotoxicity. *Journal of Neurochemistry*, 112(4), 951–962.
- Bonkale, W. L., & Austin, M. C. (2008). 3,4-Methylenedioxyamphetamine induces differential regulation of tryptophan hydroxylase 2 protein and mRNA levels in the rat dorsal raphe nucleus. *Neuroscience*, 155(1), 270–276.
- Bonni, A., Brunet, A., West, A. E., Datta, S. R., Takasu, M. A., & Greenberg, M. E. (1999). Cell survival promoted by the Ras-MAPK signaling pathway by transcription-dependent and -independent mechanisms. *Science*, 286(5443), 1358–1362.
- Cuyas, E., Robledo, P., Pizarro, N., Farre, M., Puerta, E., & Aguirre, N. (2014). 3,4-methylenedioxyamphetamine induces gene expression changes in rats related to serotonergic and dopaminergic systems, but not to neurotoxicity. *Neurotoxicity Research*, 25(2), 161–169.
- Di Benedetto, M., Bastias Candia Sdel, C., D'Addario, C., Porticella, E. E., Cavina, C., & Candeletti, S. (2011). Regulation of opioid gene expression in the rat brainstem by 3,4-methylenedioxyamphetamine (MDMA): role of serotonin and involvement of CREB and ERK cascade. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 383(2), 169–178.
- Di Benedetto, M., D'Addario, C., Candeletti, S., & Romualdi, P. (2006). Chronic and acute effects of 3,4-methylenedioxy-N-methylamphetamine ('Ecstasy') administration on the dynorphinergic system in the rat brain. *Neuroscience*, 137(1), 187–196.
- Dragunow, M., Logan, B., & Laverty, R. (1991). 3,4-Methylenedioxyamphetamine induces Fos-like proteins in rat basal ganglia: reversal with MK 801. *European Journal of Pharmacology*, 206(3), 255–258.
- Erdtmann-Vourliotis, M., Mayer, P., Riechert, U., & Holtt, V. (1999). Acute injection of drugs with low addictive potential (delta(9)-tetrahydrocannabinol, 3,4-methylenedioxyamphetamine, lysergic acid diamide) causes a much higher c-fos expression in limbic brain areas than highly addicting drugs (cocaine and morphine). *Brain Research, Molecular Brain Research*, 71(2), 313–324.
- Escobedo, I., Peraile, I., Orio, L., Colado, M. I., & O'Shea, E. (2007). Evidence for a role of Hsp70 in the neuroprotection induced by heat shock pre-treatment against 3,4-methylenedioxyamphetamine toxicity in rat brain. *Journal of Neurochemistry*, 101(5), 1272–1283.
- Eun, J. W., Kwack, S. J., Noh, J. H., Jung, K. H., Kim, J. K., & Bae, H. J. (2009). Transcriptomic configuration of mouse brain induced by adolescent exposure to 3,4-methylenedioxyamphetamine. *Toxicology and Applied Pharmacology*, 237(1), 91–101.
- Eun, J. W., Kwack, S. J., Noh, J. H., Jung, K. H., Kim, J. K., & Bae, H. J. (2010). Identification of post-generation effect of 3,4-methylenedioxyamphetamine on the mouse brain by large-scale gene expression analysis. *Toxicology Letters*, 195(1), 60–67.
- Fernandez-Castillo, N., Orejarena, M. J., Ribases, M., Blanco, E., Casas, M., & Robledo, P. (2012). Active and passive MDMA ('ecstasy') intake induces differential transcriptional changes in the mouse brain. *Genes, Brain, and Behavior*, 11(1), 38–51.
- Garcia-Osta, A., Del Rio, J., & Frechilla, D. (2004). Increased CRE-binding activity and tryptophan hydroxylase mRNA expression induced by 3,4-methylenedioxyamphetamine (MDMA, "ecstasy") in the rat frontal cortex but not in the hippocampus. *Brain Research, Molecular Brain Research*, 126(2), 181–187.
- Green, A. R., Mechan, A. O., Elliott, J. M., O'Shea, E., & Colado, M. I. (2003). The pharmacology and clinical pharmacology of 3,4-methylenedioxyamphetamine (MDMA, "ecstasy"). *Pharmacological Reviews*, 55(3), 463–508.
- Gurd, J. W. (1997). Protein tyrosine phosphorylation: implications for synaptic function. *Neurochemistry International*, 31(5), 635–649.
- Hashimoto, K., Tomitaka, S., Narita, N., Minabe, Y., & Iyo, M. (1997). Induction of Fos protein by 3,4-methylenedioxyamphetamine (Ecstasy) in rat brain: regional differences in pharmacological manipulation. *Addiction Biology*, 2(3), 317–326.
- Hatami, H., Hossainpour-Faizi, M. A., Azarfarin, M., & Azarfam, P. (2010). Chronic ecstasy use increases neurotrophin-4 gene expression and protein levels in the rat brain. *Pharmacological Reports*, 62(6), 998–1004.

- Hicks, R. R., Martin, V. B., Zhang, L., & Seroogy, K. B. (1999). Mild experimental brain injury differentially alters the expression of neurotrophin and neurotrophin receptor mRNAs in the hippocampus. *Experimental Neurology*, 160(2), 469–478.
- Kaminska, B. (2005). MAPK signalling pathways as molecular targets for anti-inflammatory therapy—from molecular mechanisms to therapeutic benefits. *Biochimica et Biophysica Acta*, 1754(1–2), 253–262.
- Karin, M. (1998). Mitogen-activated protein kinase cascades as regulators of stress responses. *Annals of the New York Academy of Sciences*, 851, 139–146.
- Kindlundh-Hogberg, A. M., Blomqvist, A., Malki, R., & Schioth, H. B. (2008). Extensive neuroadaptive changes in cortical gene-transcript expressions of the glutamate system in response to repeated intermittent MDMA administration in adolescent rats. *BMC Neuroscience*, 9, 39.
- Kindlundh-Hogberg, A. M., Pickering, C., Wicher, G., Hober, D., Schioth, H. B., & Fex Svenningsen, A. (2010). MDMA (Ecstasy) decreases the number of neurons and stem cells in embryonic cortical cultures. *Cellular and Molecular Neurobiology*, 30(1), 13–21.
- Kindlundh-Hogberg, A. M., Svenningsson, P., & Schioth, H. B. (2006). Quantitative mapping shows that serotonin rather than dopamine receptor mRNA expressions are affected after repeated intermittent administration of MDMA in rat brain. *Neuropharmacology*, 51(4), 838–847.
- Kovacs, G. G., Ando, R. D., Adori, C., Kirilly, E., Benedek, A., & Palkovits, M. (2007). Single dose of MDMA causes extensive decrement of serotonergic fibre density without blockage of the fast axonal transport in Dark Agouti rat brain and spinal cord. *Neuropathology and Applied Neurobiology*, 33(2), 193–203.
- Krishnan, V., Han, M. H., Graham, D. L., Berton, O., Renthal, W., & Russo, S. J. (2007). Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell*, 131(2), 391–404.
- Lee, S., Park, J. Y., Lee, W. H., Kim, H., Park, H. C., & Mori, K. (2009). Lipocalin-2 is an autocrine mediator of reactive astrocytosis. *Journal of Neuroscience*, 29(1), 234–249.
- Marie-Claire, C., Benturquia, N., Lundqvist, A., Courtin, C., & Noble, F. (2008). Characteristics of dual specificity phosphatases mRNA regulation by 3,4-methylenedioxymethamphetamine acute treatment in mice striatum. *Brain Research*, 1239, 42–48.
- Marie-Claire, C., Palminteri, S., Romualdi, P., & Noble, F. (2008). Effects of the selective neurotensin antagonist SR 142948A on 3,4-methylenedioxymethamphetamine-induced behaviours in mice. *Neuropharmacology*, 54(7), 1107–1111.
- Marie-Claire, C., Salzmann, J., David, A., Courtin, C., Canestrelli, C., & Noble, F. (2007). Rnd family genes are differentially regulated by 3,4-methylenedioxymethamphetamine and cocaine acute treatment in mice brain. *Brain Research*, 1134(1), 12–17.
- Martinez-Turrillas, R., Moyano, S., Del Rio, J., & Frechilla, D. (2006). Differential effects of 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) on BDNF mRNA expression in rat frontal cortex and hippocampus. *Neuroscience Letters*, 402(1–2), 126–130.
- Montiel-Duarte, C., Ansorena, E., Lopez-Zabalza, M. J., Cenarruzabeitia, E., & Iraburu, M. J. (2004). Role of reactive oxygen species, glutathione and NF-kappaB in apoptosis induced by 3,4-methylenedioxymethamphetamine (“Ecstasy”) on hepatic stellate cells. *Biochemical Pharmacology*, 67(6), 1025–1033.
- Nawata, Y., Hiranita, T., & Yamamoto, T. (2010). A cannabinoid CB(1) receptor antagonist ameliorates impairment of recognition memory on withdrawal from MDMA (Ecstasy). *Neuropsychopharmacology*, 35(2), 515–520.
- O’Donovan, K. J., Tourtellotte, W. G., Millbrandt, J., & Baraban, J. M. (1999). The EGR family of transcription-regulatory factors: progress at the interface of molecular and systems neuroscience. *Trends in Neurosciences*, 22(4), 167–173.
- Orio, L., Llopis, N., Torres, E., Izco, M., O’Shea, E., & Colado, M. I. (2010). A study on the mechanisms by which minocycline protects against MDMA (‘ecstasy’) induced neurotoxicity of 5-HT cortical neurons. *Neurotoxicity Research*, 18(2), 187–199.
- Peng, W., Premkumar, A., Mossner, R., Fukuda, M., Lesch, K. P., & Simantov, R. (2002). Synaptotagmin I and IV are differentially regulated in the brain by the recreational drug 3,4-methylenedioxymethamphetamine (MDMA). *Brain Research, Molecular Brain Research*, 108(1–2), 94–101.
- Peng, W., & Simantov, R. (2003). Altered gene expression in frontal cortex and midbrain of 3,4-methylenedioxymethamphetamine (MDMA) treated mice: differential regulation of GABA transporter subtypes. *Journal of Neuroscience Research*, 72(2), 250–258.
- Petschner, P., Tamasi, V., Adori, C., Kirilly, E., Ando, R. D., & Tothfalusi, L. (2013). Gene expression analysis indicates CB1 receptor upregulation in the hippocampus and neurotoxic effects in the frontal cortex 3 weeks after single-dose MDMA administration in Dark Agouti rats. *BMC Genomics*, 14, 930.
- Rodriguez-Alarcón, G., Canales, J. J., & Salvador, A. (2007). Rewarding effects of 3,4-ethylenedioxymethamphetamine (“Ecstasy”) in dominant and subordinate OF-1 mice in the place preference conditioning paradigm. *Prog Neuropsychopharmacol Biol Psychiatry*, 31(1), 191–199.
- Roudkenar, M. H., Halabian, R., Roushandeh, A. M., Nourani, M. R., Masroori, N., & Ebrahimi, M. (2009). Lipocalin 2 regulation by thermal stresses: protective role of Lcn2/NGAL against cold and heat stresses. *Experimental Cell Research*, 315(18), 3140–3151.
- Salzmann, J., Canestrelli, C., Noble, F., & Marie-Claire, C. (2006). Analysis of transcriptional responses in the mouse dorsal striatum following acute 3,4-methylenedioxymethamphetamine (ecstasy): identification of extracellular signal-regulated kinase-controlled genes. *Neuroscience*, 137(2), 473–482.
- Salzmann, J., Marie-Claire, C., Le Guen, S., Roques, B. P., & Noble, F. (2003). Importance of ERK activation in behavioral and biochemical effects induced by MDMA in mice. *British Journal of Pharmacology*, 140(5), 831–838.
- Shirayama, Y., Hashimoto, K., Iyo, M., Watanabe, K., Higuchi, T., & Minabe, Y. (2000). 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)-induced egr-1 mRNA in rat brain: pharmacological manipulation. *European Journal of Pharmacology*, 402(3), 215–222.
- Siuciak, J. A., Clark, M. S., Rind, H. B., Whittemore, S. R., & Russo, A. F. (1998). BDNF induction of tryptophan hydroxylase mRNA levels in the rat brain. *Journal of Neuroscience Research*, 52(2), 149–158.
- Soleimani Asl, S., Farhadi, M. H., Moosavizadeh, K., Samadi Kuchak Saraei, A., Soleimani, M., & Jamei, S. B. (2012). Evaluation of Bcl-2 family gene expression in Hippocampus of 3, 4-methylenedioxymethamphetamine treated rats. *Cell Journal*, 13(4), 275–280.
- Stephenson, C. P., Hunt, G. E., Topples, A. N., & McGregor, I. S. (1999). The distribution of 3,4-methylenedioxymethamphetamine “Ecstasy”-induced c-fos expression in rat brain. *Neuroscience*, 92(3), 1011–1023.
- Stetler, R. A., Gan, Y., Zhang, W., Liou, A. K., Gao, Y., & Cao, G. (2010). Heat shock proteins: cellular and molecular mechanisms in the central nervous system. *Progress in Neurobiology*, 92(2), 184–211.
- Stumm, G., Schlegel, J., Schafer, T., Wurz, C., Mennel, H. D., & Krieg, J. C. (1999). Amphetamines induce apoptosis and regulation of bcl-x splice variants in neocortical neurons. *FASEB Journal*, 13(9), 1065–1072.

- Thiriet, N., Ladenheim, B., McCoy, M. T., & Cadet, J. L. (2002). Analysis of ecstasy (MDMA)-induced transcriptional responses in the rat cortex. *FASEB Journal*, *16*(14), 1887–1894.
- Tiangco, D. A., Lattanzio, F. A., Jr., Osgood, C. J., Beebe, S. J., Kerry, J. A., & Hargrave, B. Y. (2005). 3,4-Methylenedioxymethamphetamine activates nuclear factor-kappaB, increases intracellular calcium, and modulates gene transcription in rat heart cells. *Cardiovascular Toxicology*, *5*(3), 301–310.
- Torres, E., Gutierrez-Lopez, M. D., Borcel, E., Peraile, I., Mayado, A., & O'Shea, E. (2010). Evidence that MDMA ('ecstasy') increases cannabinoid CB2 receptor expression in microglial cells: role in the neuroinflammatory response in rat brain. *Journal of Neurochemistry*, *113*(1), 67–78.
- Trigo, J. M., Renoir, T., Lanfumey, L., Hamon, M., Lesch, K. P., & Robledo, P. (2007). 3,4-methylenedioxymethamphetamine self-administration is abolished in serotonin transporter knockout mice. *Biological Psychiatry*, *62*(6), 669–679.
- Weber, G. F., Johnson, B. N., Yamamoto, B. K., & Gudelsky, G. A. (2014). Effects of stress and MDMA on hippocampal gene expression. *BioMed Research International*, *2014*, 141396.
- Xie, T., Tong, L., McCann, U. D., Yuan, J., Becker, K. G., & Mehan, A. O. (2004). Identification and characterization of metallothionein-1 and -2 gene expression in the context of (+/-)3,4-methylenedioxymethamphetamine-induced toxicity to brain dopaminergic neurons. *Journal of Neuroscience*, *24*(32), 7043–7050.
- Yau, J. L., Noble, J., & Seckl, J. R. (1997). Site-specific regulation of corticosteroid and serotonin receptor subtype gene expression in the rat hippocampus following 3,4-methylenedioxymethamphetamine: role of corticosterone and serotonin. *Neuroscience*, *78*(1), 111–121.
- Yuferov, V., Nielsen, D., Butelman, E., & Kreek, M. J. (2005). Microarray studies of psychostimulant-induced changes in gene expression. *Addiction Biology*, *10*(1), 101–118.

Neuropathology of DRUG ADDICTIONS AND SUBSTANCE MISUSE

Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants and International Aspects

Edited by Victor R. Preedy, BSc, PhD, DSc, FSB, FRSH, FRIPH, FRSPH, FRCPath, FRSC

Research shows that the neuropathological features of one addiction are often applicable to those of others, and understanding these commonalities provides a platform for studying specific addictions in more depth and may ultimately lead researchers toward new modes of understanding, causation, prevention, and treatment. However, marshaling data on the complex relationships between addictions is difficult owing to the myriad of materials and substances. The three volumes that make up **Neuropathology of Drug Addictions and Substance Misuse** address this challenge, offering comprehensive coverage on the adverse consequences of the most common drugs of abuse. Each volume serves to update the reader's knowledge on the broader field of addiction as well as to deepen understanding of specific addictive substances. Volume 2 addresses stimulants, club and dissociative drugs, hallucinogens, inhalants, and international aspects, with each section providing data on the general, molecular/cellular and structural/functional neurological aspects of a given substance, with a focus on the adverse consequences of addictions.

Other Volumes in the Series:

- **Neuropathology of Drug Addictions and Substance Misuse, Volume 1: Foundations of Understanding, Tobacco, Alcohol, Cannabinoids and Opioids** — ISBN: 9780128002131
- **Neuropathology of Drug Addictions and Substance Misuse, Volume 3: General Processes and Mechanisms, Prescription Medications, Caffeine and Areca, Polydrug Misuse, Emerging Addictions and Non-Drug Addictions** — ISBN: 9780128006344

About the Editor:

Victor R. Preedy is a senior member of King's College London. He is also Director of the Genomics Centre and a member of the Faculty of Life Sciences and Medicine.

Professor Preedy has longstanding academic interests in substance misuse especially in relation to health and well-being. He is a member of the Editorial Board of *Drug and Alcohol Dependence* and a founding member of the Editorial Board of *Addiction Biology*. In his career Professor Preedy was Reader at the Addictive Behaviour Centre at the University of Roehampton and also Reader at the School of Pharmacy (now part of University College London). Professor Preedy is Editor of the multivolume seminal work, **Comprehensive Handbook of Alcohol-Related Pathology** (published by Academic Press–Elsevier).

To his credit, Professor Preedy has published over 600 articles, which include peer-reviewed manuscripts based on original research, abstracts and symposium presentations, reviews and numerous books and volumes.



ACADEMIC PRESS

An imprint of Elsevier
elsevier.com

ISBN 978-0-12-800212-4



9 780128 002124