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Wolfgang H. Sommer  
Rainer Spanagel  
Editors

# Behavioral Neurobiology of Alcohol Addiction

 Springer

*Editors*

Dr. Wolfgang H. Sommer  
Institut für Psychopharmakologie  
Zentralinstitut für Seelische Gesundheit  
Mannheim  
Germany

Prof. Dr. Rainer Spanagel  
Institut für Psychopharmakologie  
Zentralinstitut für Seelische Gesundheit  
Mannheim  
Germany

ISSN 1866-3370

ISSN 1866-3389 (electronic)

ISBN 978-3-642-28719-0

ISBN 978-3-642-28720-6 (eBook)

DOI 10.1007/978-3-642-28720-6

Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2012942257

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# Preface

Dear Reader

You might think that in the age of internet and PubMed, books on current topics are outdated already ahead of publication, or that books are too sluggish in the rapid currents of information flows. At first, so did we, yet after a moment's notice one realizes that books, better than most electronic media, can provide highly needed anchoring points for looking around, taking stock, and contemplation on present scientific endeavors, and on which new direction to take. Reflecting on *Current Topics of Behavioral Neurobiology in Alcohol Addiction* was for us an orienting response, an opportunity to see our field through the eyes of many of our most esteemed colleagues and a way to engage them in discussion how alcohol can alter mood states and why this may end up becoming an addiction. With this book we hope to share ours and our contributor's excitement about the subject matter with a broad readership. Indeed, today's alcohol research generates more excitement than ever. This is visibly demonstrated by a more than threefold increase in the number of articles published in the top-notch journals of the general and multi-disciplinary science category over the last decade (Helinski and Spanagel 2011) . Naturally, the greater attention created by our field attracts new generations of students. Thus, besides contributing a comprehensive collection of reference material accompanied by critical discussions for the seasoned scholars, *Current Topics in Behavioral Neurobiology of Alcohol Addiction* aims towards new disciples in addiction research as well as interested readers from other fields of study by providing lucid presentations of these topics that are written by an assembly of highly distinguished experts and leaders in their respective research areas.

Alcohol addiction research will ultimately be judged by its ability to provide effective treatment solutions. To be successful here requires cunning and understanding far beyond Behavioral Neurobiology and other disciplines of the neurosciences including basic and clinical research, but also genetics, epidemiology, social sciences and computational approaches. Such diversity is bound to generate a constant stream of new observations and ideas that want to be pursued. Thus, our most difficult task as editors was to refrain from reviewing these latest

developments, but to select those Current Topics that have brought alcohol addiction research substantially forward and strongly influenced the thinking about it. With this idea in mind we selected five Current Topics in Behavioral Neurobiology of Alcohol Addiction which are discussed in their respective parts of the book.

The part I deals with the conceptualization of addiction and underlying neurobiological mechanisms. This topic is important because there is an ongoing debate about the role of the mesolimbic dopamine system in driving and maintaining addictive behaviors, especially for alcohol addiction. Further, exciting new concepts such as the glutamate theory of addiction or the importance of anti-reward systems have emerged and driven new investigation into the cellular and synaptic consequence of alcohol exposure.

The part II takes up genetic approaches which in the last decade have enormously influenced psychiatric research. Notable, with the early accomplishment of genome-wide association studies (GWAS) and the emergence of candidate genes derived from cohorts of tens of thousands of subjects the alcohol field has been in the forefront of psychiatric genetics. Here, the new insights from genome-wide studies in humans and experimental animals are discussed in view of their ramifications for understanding alcohol use disorder as a diagnostic entity in current systems of psychiatric diagnoses. Chapters on the influence of genetic factors on alcohol behaviors in non-human species supplement this part. Given the ever more sophisticated techniques for genetic manipulations and the large number of genes that may influence alcohol behaviors we found it justified to invite a new review on genetically modified mouse models, the latest being completed already six years ago<sup>2</sup>.

The part III takes a look at the broad range of procedures for testing new and existing hypotheses about addictive behaviors in appropriate animal experiments and more recently in the human laboratory. Concerning animal models there is an apparent shift towards much longer duration of alcohol exposure reflecting the increased emphasis on the chronic progressive course of addiction and the drive to discover pathology-related long-term neuroadaptations underlying it.

Another area of great development is neuroimaging which is considered in part IV of this volume. Although a relatively novel tool for studying the human brain, we may already conclude that many human neuroimaging experiments recapitulate our knowledge from animal studies about the neurocircuitry involved in the action of alcohol and addiction, and in this way are giving much needed validity to our animal models. Imaging responses specific to the human disorder or translatable between humans and animals may hold promises for identification of easily accessible biomarkers for treatment development.

The part V of the book is dedicated to translational approaches for treatment development in alcohol addiction. Although many researchers in the field may feel that they always had a translational perspective to the subject matter, the last decade has truly put the focus on the need of translating knowledge gained from basic results more rapidly into clinical developments. The term “translational research” is in our mind not a mere buzz-word, rather the stringent application of

this concept has truly brought our field forward. Although, no new therapeutics could be introduced into clinical practice in recent years, the examples presented here, ranging from psychotherapy to pharmacology to neurosurgery, demonstrate the power of the translational approach and raise hopes that the dire situation of alcoholic patients can be changed in the near future.

Finally, we deeply thank all our contributors for the enthusiasm, dedication and patience they have invested into this project and into us, because working for a book like the present one can only be seen as an act of great passion for science. We are humbled by their altruism and collegiality evident by the near lack of any reward expectation, neither monetary nor impact points wise, to offset the time and trouble that undeniably has to be laid down into such an endeavor. We are grateful to the Springer team for their encouragement, help and endurance in publishing this book.

Mannheim, Germany

Wolfgang Sommer  
Rainer Spanagel

## References

- Helinski S, Spanagel R (2011) Publication trends in addiction research. *Addict Biol.*16(4):532  
Crabbe JC et al (2006) Alcohol-related genes: contributions from studies with genetically engineered mice. *Addict Biol.*11(3-4):195

# Contents

## Part I Mechanistic Aspects Underlying Alcoholism

<b>Theoretical Frameworks and Mechanistic Aspects of Alcohol Addiction: Alcohol Addiction as a Reward Deficit Disorder . . . . .</b>	<b>3</b>
George F. Koob	
<b>Synaptic Effects Induced by Alcohol . . . . .</b>	<b>31</b>
David M. Lovinger and Marisa Roberto	
<b>Signaling Pathways Mediating Alcohol Effects . . . . .</b>	<b>87</b>
Dorit Ron and Robert O. Messing	
<b>Neurocircuitry Involved in the Development of Alcohol Addiction: The Dopamine System and its Access Points. . . . .</b>	<b>127</b>
Bo Söderpalm and Mia Ericson	
<b>What is in that Drink: The Biological Actions of Ethanol, Acetaldehyde, and Salsolinol . . . . .</b>	<b>163</b>
Gerald A. Deehan Jr., Mark S. Brodie and Zachary A. Rodd	

## Part II Genetics

<b>Modeling the Diagnostic Criteria for Alcohol Dependence with Genetic Animal Models . . . . .</b>	<b>187</b>
John C. Crabbe, Kenneth S. Kendler and Robert J. Hitzemann	
<b>Non-Human Primate Models of Alcohol-Related Phenotypes: The Influence of Genetic and Environmental Factors . . . . .</b>	<b>223</b>
Christina S. Barr	



<b>Genetically Selected Alcohol Preferring Rats to Model Human Alcoholism</b> . . . . .	251
Roberto Ciccocioppo	
<b>Advanced Transgenic Approaches to Understand Alcohol-Related Phenotypes in Animals</b> . . . . .	271
Ainhoa Bilbao	
<b>Part III Clinical Phenotypes and Preclinical Models Thereof</b>	
<b>Modeling Alcohol Self-Administration in the Human Laboratory</b> . . . .	315
Ulrich S. Zimmermann, Sean O'Connor and Vijay A. Ramchandani	
<b>Animal Models of Excessive Alcohol Consumption in Rodents</b> . . . . .	355
Howard C. Becker	
<b>Modeling Relapse Situations in the Human Laboratory</b> . . . . .	379
Rajita Sinha	
<b>Modeling Relapse in Animals</b> . . . . .	403
Rémi Martin-Fardon and Friedbert Weiss	
<b>Invertebrate Models of Alcoholism.</b> . . . .	433
Henrike Scholz and Julie A. Mustard	
<b>Part IV Novel Insights from Brain Imaging</b>	
<b>The Dopamine System in Mediating Alcohol Effects in Humans</b> . . . . .	461
K. Charlet, A. Beck and A. Heinz	
<b>Stimulant and Sedative Effects of Alcohol</b> . . . . .	489
Reuben A. Hendler, Vijay A. Ramchandani, Jodi Gilman and Daniel W. Hommer	
<b>Chronic Alcohol Consumption, Abstinence and Relapse: Brain Proton Magnetic Resonance Spectroscopy Studies in Animals and Humans</b> . . . . .	511
Dieter J. Meyerhoff, Timothy C. Durazzo and Gabriele Ende	

**Part V Translational Aspects and Medication Development**

**Translational Approaches to Medication Development . . . . .** 543  
Selena Bartlett and Markus Heilig

**New Pharmacological Treatment Strategies  
for Relapse Prevention . . . . .** 583  
Rainer Spanagel and Valentina Vengeliene

**The Challenge of Studying Parallel Behaviors in Humans  
and Animal Models . . . . .** 611  
David N. Stephens, Hans S. Crombag and Theodora Duka

**A Translational Approach to Novel Medication Development  
for Protracted Abstinence . . . . .** 647  
Barbara J. Mason and Amanda E. Higley

**New Approaches to Addiction Treatment Based on Learning  
and Memory . . . . .** 671  
Falk Kiefer and Christina Dinter

**Adolescent Substance Misuse: Neurobiology and Evidence-Based  
Interventions . . . . .** 685  
Nicola C. Newton, Maeve O’Leary-Barrett and Patricia J. Conrod

**Deep Brain Stimulation as a Therapy for Alcohol Addiction. . . . .** 709  
Thomas F. Münte, Hans-Jochen Heinze and Veerle Visser-Vandewalle