

N INTERNATIONAL REVIEW OF NEUROBIOLOGY

THE ROLE OF NEUROPEPTIDES IN ADDICTION AND
DISORDERS OF EXCESSIVE CONSUMPTION

VOLUME 136



EDITED BY
TODD E. THIELE





VOLUME ONE HUNDRED AND THIRTY SIX

INTERNATIONAL REVIEW OF NEUROBIOLOGY

The Role of Neuropeptides in Addiction
and Disorders of Excessive
Consumption

Edited by

TODD E. THIELE

*University of North Carolina at Chapel Hill,
Chapel Hill, NC, United States*



ACADEMIC PRESS

An imprint of Elsevier

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

First edition 2017

Copyright © 2017 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.

ISBN: 978-0-12-812473-4

ISSN: 0074-7742

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



**Working together
to grow libraries in
developing countries**

www.elsevier.com • www.bookaid.org

Publisher: Zoe Kruze

Acquisition Editor: Sam Mahfoudh

Editorial Project Manager: Andrea Gallego Ortiz

Production Project Manager: Vignesh Tamil

Cover Designer: Victoria Pearson

Typeset by SPi Global, India



VOLUME ONE HUNDRED AND THIRTY SIX

INTERNATIONAL REVIEW OF NEUROBIOLOGY

**The Role of Neuropeptides in Addiction
and Disorders of Excessive
Consumption**

INTERNATIONAL REVIEW OF NEUROBIOLOGY

VOLUME 136

SERIES EDITOR

PATRICIA JANAK

*Janak Lab, Dunning Hall
Baltimore, MD, USA*

PETER JENNER

*Division of Pharmacology and Therapeutics
GKT School of Biomedical Sciences
King's College, London, UK*

EDITORIAL BOARD

ERIC AAMODT

PHILIPPE ASCHER

DONARD S. DWYER

MARTIN GIURFA

PAUL GREENGARD

NOBU HATTORI

DARCY KELLEY

BEAU LOTTO

MICAELA MORELLI

JUDITH PRATT

EVAN SNYDER

JOHN WADDINGTON

HUDA AKIL

MATTHEW J. DURING

DAVID FINK

BARRY HALLIWELL

JON KAAS

LEAH KRUBITZER

KEVIN MCNAUGHT

JOSÉ A. OBESO

CATHY J. PRICE

SOLOMON H. SNYDER

STEPHEN G. WAXMAN

CONTRIBUTORS

Jessica R. Barson

Drexel University College of Medicine, Philadelphia, PA, United States

Mehdi Farokhnia

Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, National Institute on Alcohol Abuse and Alcoholism and National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, United States

William J. Giardino

Stanford University, Stanford, CA, United States

Markus Heilig

Center for Social and Affective Neuroscience, Linkoping University, Linkoping, Sweden

Katherine M. Holleran

Wake Forest School of Medicine, Winston-Salem, NC, United States

Sara R. Jones

Wake Forest School of Medicine, Winston-Salem, NC, United States

Anushree Karkhanis

Wake Forest School of Medicine, Winston-Salem, NC, United States

Dean Kirson

The Scripps Research Institute, La Jolla, CA, United States

Lorenzo Leggio

Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, National Institute on Alcohol Abuse and Alcoholism and National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD; Center for Alcohol and Addiction Studies, Brown University, Providence, RI, United States

Sarah F. Leibowitz

The Rockefeller University, New York, NY, United States

Montserrat Navarro

University of North Carolina, Chapel Hill, NC, United States

Cort A. Pedersen

The University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Marisa Roberto

The Scripps Research Institute, La Jolla, CA, United States

Stacey L. Robinson

University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Andrey E. Ryabinin

Oregon Health & Science University, Portland, OR, United States

Jesse R. Schank

University of Georgia, Athens, GA, United States

Samantha R. Spierling

The Scripps Research Institute, La Jolla, CA, United States

Todd E. Thiele

University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Brendan J. Tunstall

Neurobiology of Addiction Section, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, United States

Leandro F. Vendruscolo

Neurobiology of Addiction Section, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, United States

Lia J. Zallar

Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, National Institute on Alcohol Abuse and Alcoholism and National Institute on Drug Abuse, National Institutes of Health, Bethesda; Neurobiology of Addiction Section, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, United States

Eric P. Zorrilla

The Scripps Research Institute, La Jolla, CA, United States

PREFACE

Centrally acting neuropeptides modulate a diverse array of neurobiological functions, including consummatory and ingestive behaviors that are critical for survival. Many neuropeptides modulate the intake of both natural rewards (i.e., those necessary for survival such as food and water) and the consumption of drugs and alcohol. When the actions of these neuropeptides are imbalanced, the result can translate into excessive consumption that threatens the well-being of the organism. Interestingly, in many cases, repeated consumption of food, drugs, and alcohol can promote alterations in neuropeptide systems, which in turn drive increased consumption and further neuropeptide imbalance. This vicious cycle is thought to underlie the transition to drug and alcohol dependence, as well as eating disorders. Thus, targeting neuropeptide systems as therapeutic treatments for disorders of excessive consumption is a promising approach.

The goal of this volume is to highlight some of the most well-studied neuropeptide systems that modulate consumption of drugs, alcohol, and, in some cases, food. I would like to take this opportunity to thank the authors that have taken the time to provide outstanding chapters for this book. After a brief introduction in Chapter 1, Marisa Roberto, Samantha Spierling, Dean Kirson, and Eric Zorrilla in Chapter 2 describe the role of elevated corticotropin-releasing factor (CRF) signaling in modulating negative emotional states that emerge with drug and alcohol dependence, which in turn drives excessive intake through negative reinforcement, a process referred to as the “dark side” of addiction. The role of CRF in compulsive eating disorders is also discussed. In Chapter 3, Anushree Karkhanis, Katherine Holleran, and Sara Jones describe the role of the dynorphin/kappa opioid receptor (KOR) system in modulating the “dark side” of addiction. Like CRF, dynorphin/KOR signaling is upregulated with drug and alcohol dependence which produces a negative emotional state that motivates excessive drug and alcohol intake via negative reinforcement. The dynorphin/KOR system modulates excessive consumption, in part, by blunting dopamine signaling in the brain. In Chapter 4, Lia Zallar, Mehdi Farokhnia, Brendan Tunstall, Leandro Vendruscolo, and Lorenzo Leggio describe the role of the gut peptide, ghrelin, in modulating drug and alcohol intake. Ghrelin acts centrally and has been implicated in both feeding and drug and alcohol use in both preclinical and clinical studies. In Chapter 5,

Montserrat Navarro describes the role of the melanocortin (MC) system in modulating drug and alcohol consumption. For many years the role of the MC system has been studied with respect to food intake and obesity, and the work by Navarro highlights the role of this system in modulating excessive alcohol intake. Given the overlapping control of feeding and alcohol intake, therapeutic drugs aimed at the MC may be useful for treating both obesity and alcohol use disorders. In Chapter 6, Jesse Schank and Markus Heilig describe the role of substance P (SP) and the associated neurokinin-1 receptor (NK1R) in treating alcohol use disorders. They compare SP and the NK1R to the CRF system and provide evidence that NK1R antagonists may have therapeutic value for treating addiction. In Chapter 7, Stacey Robinson and myself overview evidence for a role for neuropeptide Y (NPY) in modulating drug and alcohol use disorders. Repeated drug and alcohol use is associated with reduced NPY signaling in brain regions that modulate emotion which triggers a negative emotional state and increased drug and alcohol intake via negative reinforcement. Thus, like many of the neuropeptides described earlier, therapeutic targets aimed at the NPY system may have value for treating the “dark side” of addiction. In Chapter 8, Jessica Barson and Sarah Leibowitz discuss the role of the hypothalamic neuropeptide, orexin/hypocretin (OX). They describe how OX signaling in the hypothalamus is involved in modulating intake of natural rewards that maintain homeostasis, and how OX signaling outside of the hypothalamus can modulate the intake of alcohol and drugs of abuse. Interestingly, drugs and alcohol stimulate OX signaling which they suggest promotes abuse through a positive feedback loop. In Chapter 9, Cort Pedersen describes the role of oxytocin in modulating drug and alcohol use. Clinical trial evidence suggests that intranasal oxytocin blunts withdrawal responses and reduces alcohol consumption in heavy drinkers. It is hypothesized that oxytocin may reduce alcohol intake by reversing tolerance. Finally, in Chapter 10, Andrey Ryabinin and William Giardino describe the contribution of the urocortin system in alcohol use disorders. Interestingly, urocortin neuropeptides act on CRF receptors and thus are part of the CRF system. They overview evidence, indicating that urocortin 1 modulates excessive alcohol intake.

Once again, I am very grateful to my colleagues for all the time and effort they dedicated to this volume. It is my hope that this volume will impress the reader with the significant role that neuropeptides play in modulating disorders of excessive consumption.

TODD E. THIELE
University of North Carolina at Chapel Hill

CONTENTS

<i>Contributors</i>	<i>ix</i>
<i>Preface</i>	<i>xi</i>
1. Neuropeptides and Addiction: An Introduction	1
Todd E. Thiele	
2. Corticotropin-Releasing Factor (CRF) and Addictive Behaviors	5
Marisa Roberto, Samantha R. Spierling, Dean Kirson, and Eric P. Zorrilla	
1. Introduction	6
2. CRF Stress Systems	7
3. CRF, the HPA Axis, and Addiction	8
4. Extrahypothalamic CRF Systems	10
5. Role for CRF–CRF ₁ Systems in Animal Models of Addiction	11
6. Central Extended Amygdala	14
7. Ventral Tegmental Area	24
8. Prefrontal Cortex	28
9. Compulsive Eating	28
10. Conclusion	31
Acknowledgments	31
References	31
3. Dynorphin/Kappa Opioid Receptor Signaling in Preclinical Models of Alcohol, Drug, and Food Addiction	53
Anushree Karkhanis, Katherine M. Holleran, and Sara R. Jones	
1. Introduction	54
2. Ethanol and Kappa Opioid Receptors	62
3. Cocaine and Kappa Opioid Receptors	68
4. Obesity and Kappa Opioid Receptors	73
5. Kappa Opioid Receptor-Based Therapeutics	77
References	80
Further Reading	88

4. The Role of the Ghrelin System in Drug Addiction	89
Lia J. Zallar, Mehdi Farokhnia, Brendan J. Tunstall, Leandro F. Vendruscolo, and Lorenzo Leggio	
1. Introduction	90
2. Ghrelin and Alcohol	93
3. Ghrelin and Stimulants	100
4. Ghrelin and Tobacco/Nicotine	102
5. Ghrelin and Opioids	104
6. Ghrelin and Cannabis	105
7. Conclusions	106
Acknowledgments and Disclosures	108
References	108
5. The Role of the Melanocortin System in Drug and Alcohol Abuse	121
Montserrat Navarro	
1. Introduction	122
2. Melanocortin Receptors	123
3. Melanocortins and Drugs of Abuse	128
4. Melanocortins and Ethanol	129
5. The Role of MC3R and MC4R in the Modulation of Ethanol Consumption	133
6. Targeting the MCRs to Treat Alcohol Abuse Disorders	137
References	139
6. Substance P and the Neurokinin-1 Receptor: The New CRF	151
Jesse R. Schank and Markus Heilig	
1. Introduction	152
2. Basic Characteristics of the SP/NK1R System	152
3. Preclinical Findings on SP and NK1R	155
4. Mechanisms of Action: Monoamine Signaling and Interactions With Other Transmitters	162
5. Clinical Research	165
6. Summary and Conclusions	167
References	169
7. The Role of Neuropeptide Y (NPY) in Alcohol and Drug Abuse Disorders	177
Stacey L. Robinson and Todd E. Thiele	
1. Introduction	178
2. NPY System and Genetic Predisposition to Ethanol Use	179
3. Ethanol Impact on the NPY System	181

4. The Impact of NPY System Manipulation on Ethanol-Directed Behaviors	182
5. NPY System and Other Drugs of Abuse	184
6. Translational Relevance	188
7. Conclusion	189
Acknowledgments	190
References	190
 8. Orexin/Hypocretin System: Role in Food and Drug Overconsumption	 199
Jessica R. Barson and Sarah F. Leibowitz	
1. Introduction	200
2. Anatomy of Orexin/Hypocretin-Expressing Neurons	200
3. Role of Orexin/Hypocretin in Homeostatic Feeding and Other Adaptive Behaviors	204
4. Role of Orexin/Hypocretin in Nonhomeostatic Intake	207
5. Conclusions	222
Acknowledgments	223
References	223
 9. Oxytocin, Tolerance, and the Dark Side of Addiction	 239
Cort A. Pedersen	
1. Intranasal Oxytocin Treatment of Alcohol Withdrawal	243
2. Intranasal Oxytocin Treatment Effects on Alcohol Consumption in Heavy Drinkers	246
3. Implications of Our Preliminary Findings	248
4. Additional Human Studies	250
5. Pioneering Studies of Oxytocin Effects on Tolerance Formation and Established Tolerance to Alcohol, Opioids, and Cocaine	253
6. Newer Animal Studies on Oxytocin and Addiction	258
7. Commentary on the Interpretation of Recent Animal Study Findings on Oxytocin and Addiction	262
8. Oxytocin, Social Bonds, and Addiction	264
9. Final Comments	265
References	266
 10. Contribution of Urocortin to the Development of Excessive Drinking	 275
Andrey E. Ryabinin and William J. Giardino	
1. Introduction: The Promise of the CRF System	276
2. The CRF/Urocortin System	277

3. Complications of Studying Actions of CRF and Ucn1	278
4. Alcohol Sensitivity of the Ucn1 Neuropeptide System	279
5. Genetic Associations of the EWcp Ucn1 System With Excessive Alcohol Consumption	280
6. Effects of Excessive Alcohol Consumption on the Ucn1 System and EWcp	281
7. Effects of Genetic Manipulations of EWcp Ucn1 System on Alcohol Consumption	282
8. The Critical Role of the EWcp Ucn1 System in Excessive Alcohol Consumption	283
9. Contrasting the Roles of Ucn1 vs CRF in Contribution to Excessive Alcohol Consumption	284
Acknowledgments	287
References	287



Neuropeptides and Addiction: An Introduction

Todd E. Thiele¹

University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

¹Corresponding author: e-mail address: thiele@unc.edu

Abstract

Neuropeptides are short sequences of amino acids that are coexpressed with neurotransmitters and which are widely expressed throughout the central nervous system. There is a large database of data pointing to critical roles for neuropeptides in modulating neurobiological responses to alcohol and drugs of abuse. Continued alcohol and drug use promote allostatic alterations in neuropeptide systems, and these changes contribute to excessive and uncontrolled intake that emerges with dependence. The neuropeptides that are reviewed in this chapter represent some of the most well-studied targets in the current drug and alcohol abuse literature. The goal of this chapter is to convey the significant roles that neuropeptides play in neurobiological responses to alcohol and drugs of abuse, and reinforce the idea that targeting neuropeptides and their receptors continue to be attractive avenues for treating drug and alcohol use disorders, as well as eating disorders.

The goal of this chapter is to provide the reader with an appreciation for the critical role that central neuropeptides play in modulating disorders of excessive consumption, including drug and alcohol abuse and eating disorders. Neuropeptides are short sequences of amino acids, typically defined as having 50 base pairs or less (with large sequences referred to as proteins). Neuropeptides are widely distributed throughout the central nervous system and are cosecreted from neurons with small-molecule neurotransmitters, including glutamate and gamma-aminobutyric acid. Neuropeptides can function as neuromodulators, influencing the synaptic transmission of cosecreted small-molecule neurotransmitters, as well as neurotransmitters. Generally, neuropeptides act on G protein-coupled receptors that are expressed pre- and postsynaptically, often depending on receptor subtype (for a recent review on neuropeptides, see van den Pol, 2012). There are numerous neuropeptides expressed throughout the brain with unique expression and projection patterns. In many cases, specific neuropeptides appear to be involved

with diverse sets of neurobiological functions, depending on the brain region of action. For example, numerous neuropeptides arise from the hypothalamus and help maintain physiological homeostasis and energy balance by modulating motivated behaviors aimed at acquiring natural reinforcers, such as food and water (Zeltser, Seeley, & Tschoop, 2012). These hypothalamic neuropeptides can act locally within the hypothalamus, or project to other regions to interact with other systems, such as the mesolimbic dopamine reward system (Roseberry, Stuhman, & Dunigan, 2015) which modulates the reinforcing properties of drugs and natural reward. Other neuropeptides are produced within the extended amygdala, an interconnected and functionally similar set of brain regions critical for integrating emotional behaviors (Koob & Le Moal, 2001). Here again, neuropeptides can function locally within the extended amygdala or project to, and interact with, other system.

A growing body of literature has emerged indicating important roles for neuropeptides in modulating neurobiological responses to alcohol and other drugs of abuse, and several of these neuropeptides are described in the following chapters. Repeated drug and alcohol abuse are thought to produce plastic alterations in neuropeptide systems, creating allostatic shifts in activity and function, above or below, homeostatic levels maintained under baseline conditions (Koob & Le Moal, 2001). Alterations of neuropeptide activity, in systems such as those that modulate energy balance, reward, or emotional responses, are thought to contribute to escalating drug and alcohol use as one transitions to dependence. Years ago we proposed the idea that overlapping neuropeptide systems may modulate excessive alcohol intake and eating disorders, based on converging evidence that numerous neuropeptide systems were similarly influence by ethanol drinking and energy balance, and that manipulating these systems similarly influence ethanol intake and feeding (Thiele et al., 2003). These observations raise the interesting possibility that neuropeptides involved with feeding and alcohol intake influence the consumption of these stimuli through modulation of their reinforcing properties. Interestingly, every neuropeptide reviewed in this chapter has been implicated in modulating both feeding behavior and consumption or seeking of drugs/alcohol.

Drug- and alcohol-induced alterations of neuropeptide systems within the extended amygdala promote dysregulation of emotions which contributes to a negative affective state (associated with symptoms such as anxiety and depression) that is characteristic to those dependent on drugs or alcohol,

particularly during withdrawal. Negative affect, in turn, is thought to motivate drug and alcohol intake as a way to reduce these adverse symptoms (an example of negative reinforcement), reflecting excessive drug and alcohol intake stemming from dependence (Koob & Le Moal, 2001). Finally, neuropeptides have been implicated in other neurobiological responses to drugs and alcohol that have been proposed to influence their intake, including sensitivity to the drug's intoxicating effects (Schuckit, 2009) and the modulation of pain (Egli, Koob, & Edwards, 2012).

While it would not be practical to review all neuropeptides involved, the neuropeptides that are reviewed in this chapter represent some of the most well-studied targets in the current drug and alcohol abuse literature. We hope that this chapter will convey the significant roles that neuropeptides play in neurobiological responses to alcohol and drugs of abuse, and reinforce the idea that targeting neuropeptides and their receptors continue to be attractive avenues for treating drug and alcohol use disorders, as well as eating disorders.

REFERENCES

- Egli, M., Koob, G. F., & Edwards, S. (2012). Alcohol dependence as a chronic pain disorder. *Neuroscience and Biobehavioral Reviews*, 36(10), 2179–2192. <http://dx.doi.org/10.1016/j.neubiorev.2012.07.010>.
- Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, 24(2), 97–129.
- Roseberry, A. G., Stuhrman, K., & Dunigan, A. I. (2015). Regulation of the mesocorticolimbic and mesostriatal dopamine systems by alpha-melanocyte stimulating hormone and agouti-related protein. *Neuroscience and Biobehavioral Reviews*, 56, 15–25. <http://dx.doi.org/10.1016/j.neubiorev.2015.06.020>.
- Schuckit, M. A. (2009). An overview of genetic influences in alcoholism. *Journal of Substance Abuse Treatment*, 36(1), S5–14.
- Thiele, T. E., Navarro, M., Sparta, D. R., Fee, J. R., Knapp, D. J., & Cubero, I. (2003). Alcoholism and obesity: Overlapping neuropeptide pathways? *Neuropeptides*, 37, 321–337.
- van den Pol, A. N. (2012). Neuropeptide transmission in brain circuits. *Neuron*, 76(1), 98–115. <http://dx.doi.org/10.1016/j.neuron.2012.09.014>.
- Zeltser, L. M., Seeley, R. J., & Tschop, M. H. (2012). Synaptic plasticity in neuronal circuits regulating energy balance. *Nature Neuroscience*, 15(10), 1336–1342. <http://dx.doi.org/10.1038/nn.3219>.

