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The Role of Neuropeptides in Addiction and Disorders of Excessive Consumption

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Todd E. Thiele

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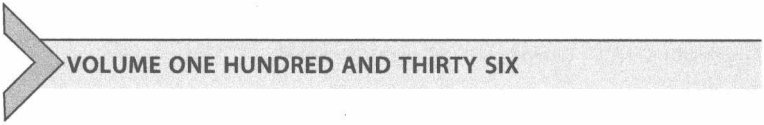

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PREFACE

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.

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CONTENTS

CHAPTER ONE

Neuropeptides and Addiction: An Introduction

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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

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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 reinforces, such as food and water (Zeltser, Seeley, & Tschop, 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, Stuhrman, & 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.

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