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Brain pathways to recovery from alcohol dependence

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ABSTRACT

This article highlights the research presentations at the satellite symposium on "Brain Pathways to Recovery from Alcohol Dependence" held at the 2013 Society for Neuroscience Annual Meeting. The purpose of this symposium was to provide an up to date overview of research efforts focusing on understanding brain mechanisms that contribute to recovery from alcohol dependence. A panel of scientists from the alcohol and addiction research field presented their insights and perspectives on brain mechanisms that may underlie both recovery and lack of recovery from alcohol dependence. The four sessions of the symposium encompassed multilevel studies exploring mechanisms underlying relapse and craving associated with sustained alcohol abstinence, cognitive function deficit and recovery, and translational studies on preventing relapse and promoting recovery. Gaps in our knowledge and research opportunities were also discussed.

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Introduction

Extensive research efforts have focused on understanding neurobiological mechanisms underlying alcohol dependence. Relatively little attention, however, has been directed at understanding the neurobiology of recovery from alcohol dependence. Epidemiological data suggest that, among people who are alcohol dependent prior-to-past year, 18.2% could maintain abstinence, suggesting the potential of recovery from alcohol dependence (Dawson et al., 2005). Although the number of studies is limited, evidence from both human and animal studies suggests that recovery from alcohol dependence is a dynamic process and that differential brain functional and behavioral changes are associated with different stages of abstinence. The mechanisms underlying these changes, their temporal course, and the degree to which these changes influence recovery or relapse require careful studies.

Abbreviations: CeA, central amygdala; CRF, corticotropin-releasing factor; PFC, prefrontal cortex; NAc, nucleus accumbens; HPA, hypothalamic-pituitary-adrenal; TLR, Toll-like Receptor.

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Alcohol withdrawal produces a constellation of symptoms and is associated with changes in gene regulation, neuronal activity, and behavior. Although a few studies have demonstrated these dynamic changes during early to protracted abstinence, little is known about how these changes impact recovery. To gain a significant understanding of brain pathways underlying recovery, multi-level studies are needed to address changes in various neurobiological systems and behaviors during protracted abstinence. Successful recovery has recently been associated with changes in alcohol-induced neuroadaptation and brain network rewiring. However, it remains not understood how sustained alcohol abstinence alters adaptation of neurocircuits driving dependence and how targeted modulations of these neural pathways disrupt alcohol-associated memory, improve cognitive recovery, and impact other parameters, such as sleep dysregulation during abstinence. Thus, studies are needed to understand neurobiological mechanisms underlying recovery. Lastly, integrating animal models and human studies that target affected neural circuitry should facilitate the translation of basic research discovery and help to identify effective treatment strategies to ameliorate the devastating consequences of alcoholism. This symposium was sponsored by NIAAA and organized by the Division of Neuroscience and Behavior at NIAAA. At the symposium, Dr. Kenneth Warren highlighted the recent progress in alcohol neuroscience research, and Dr. Changhai Cui gave an introduction overview on brain pathways to recovery from alcohol dependence. Speakers Drs. George Koob, Rajita Sinha, Mahesh Thakkar, Fulton Crews, Judson Chandler, Adolf Pfefferbaum, Howard Becker, David Lovinger, Barry Everitt, Chitra Mandyam, George Fein, and Marc Potenza presented selections of their studies on neurobiological and behavioral changes associated with alcohol dependence, abstinence, relapse, and recovery, and highlighted potential behavioral and therapeutic strategies to aid the recovery process. Dr. Edith Sullivan moderated the panel discussion, and the panelists, including Drs. Kathleen Grant, Adron Harris, Dieter Meyerhoff, Marisa Roberto, and Edith Sullivan, provided insightful discussions into the presentations, discussed research gaps, and suggested future research directions.

Symposium Agenda:

Introduction

Negative Affect Associated with Alcohol Abstinence

Compulsive alcohol seeking driven by the negative emotional states associated with alcohol abstinence
George F. Koob

Disrupted stress-related medial prefrontal cortex / anterior cingulate cortex activity jeopardizes alcohol recovery
Rajita Sinha

Impaired sleep homeostasis is the cause of sleep disruptions associated with alcoholism
Mahesh Thakkar

Cognitive Function Deficit and Recovery

Persistent increases in Toll-like Receptor signaling and reversal learning deficits in abstinence
Fulton T. Crews

Plasticity of the medial prefrontal cortex and deficits in executive function following chronic alcohol exposure
L. Judson Chandler

Dynamic course of alcoholism: brain imaging of humans and animal models
Adolf Pfefferbaum

Neuroadaptation During Abstinence

Genetic influences and gene expression changes associated with alcohol dependence, withdrawal, and relapse drinking
Howard C. Becker

Striatal adaptations that are associated with relapse drinking during early and protracted abstinence
David Lovinger

Promoting abstinence by decreasing the impact of drug-associated memories through reconsolidation blockade
Barry J. Everitt

Neuromechanisms of Treatment

Relationship between cortical gliogenesis and alcohol-use disorders: new avenues for novel therapies
Chitra D. Mandyam

Resting-state synchrony: a potential neurofeedback target-oriented treatment for alcoholism
George Fein

Using neuroimaging approaches to understand treatment mechanisms
Marc N. Potenza

Discussion

Kathy Grant, Adron Harris, Dieter Meyerhoff, Marisa Roberto, and Edith V. Sullivan

Negative affect associated with alcohol abstinence

Compulsive alcohol seeking driven by the negative emotional states associated with alcohol abstinence

George F. Koob

Addiction to drugs or alcohol can be defined as a chronic, relapsing disorder that has been characterized by (*i*) a compulsion to seek and take drugs, (*ii*) the loss of control over drug intake, and (*iii*) the emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) that defines a motivational withdrawal syndrome when access to the drug is prevented (Koob & Le Moal, 1997). Addiction has been conceptualized as a three-stage cycle – *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation* – that worsens over time and involves allostatic changes in the brain reward and stress systems that lead to compulsive alcohol taking and seeking. Two primary sources of reinforcement, positive and negative reinforcement, have been hypothesized to play a role in this allostatic process (Koob & Le Moal, 2001, 2008). Positive reinforcement is defined as the process by which the presentation of a stimulus increases the probability of a response. Negative reinforcement is defined as the process by which the removal of an aversive stimulus (or aversive state in the case of addiction) increases the probability of a response (Koob, 2013).

The focus of the present treatise is on the *withdrawal/negative affect* stage and a specific role for the brain stress systems in negative reinforcement. The brain stress systems can be defined as neurochemical systems that are activated during exposure to acute stressors or in a chronic state of stress and mediate species-typical behavioral responses. Key neurotransmitter systems with circumscribed neurocircuitry that mediates behavioral responses to stressors include the hypothalamic-pituitary-adrenal (HPA) axis with glucocorticoids and extrahypothalamic stress systems with corticotropin-releasing factor (CRF) (Koob, 2008). Corticotropin-releasing factor