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Editors

The Neuropharmacology of Alcohol

Springer

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Preface

This volume of the *Handbook of Experimental Pharmacology*, "The Neuropharmacology of Alcohol," was an exciting and challenging editorial effort. Our understanding of the pharmacology of the simple organic compound ethanol (referred to as alcohol in this volume) has flourished in the past 40 years. This volume focuses on the alcohol's central nervous system (CNS) effects and its behavioral pharmacology related to abuse potential. Many of alcohol's initial actions on brain targets that were identified in the late 1980s and early 1990s have stood the test of time and technological developments; however, far more depth and breadth has been added to our understanding of alcohol's pharmacology in the past two decades. With this reality in mind, it was difficult to assemble 20 of the most important topics for this volume. There are regrettable gaps in the neurotransmitter systems covered and the extent of phenotypic outcomes related to chronic alcohol exposure. Nevertheless, representative mechanisms of alcohol's neuropharmacology are presented, we hope to the satisfaction of the interested reader. We have organized the volume by general emphasis on neurotransmitter systems, neuropeptides, and ion channels as well as newer topics including neuroimmune systems, genomic mechanisms, and a current review of preclinical animal and human clinical studies of pharmacotherapy developments.

The gamma-aminobutyric acid (GABA) and glutamatergic systems were arguably the first receptor systems found to have the sensitivity and selectivity expected for receptor-mediated alcohol outcomes. These amino acid neurotransmitters continue to be the most studied in alcohol neuropharmacology. Furthermore, as the field continues to define both pre- and postsynaptic mechanisms, neuroanatomical specificity and GABA–glutamate interactions are becoming prominent explanations of alcohol's behavioral effects. Therefore, we highlight these recent developments with five chapters. A general overview of $GABA_A$-gated chloride channels as a target of alcohol is provided by Chandler, Overton, Ruedi-Bettschen, and Platt. This is complemented by a chapter by Lovinger on presynaptic release mechanisms implicated in G-protein coupled receptor actions on GABAeric synapses. Notable is the range of brain areas where alcohol's effects appear to alter synaptic efficacy and the potential cross talk with other drugs of abuse. The importance of alcohol's interaction with neurosteroid $GABA_A$ networks is reviewed by Finn and Jimenez. The chapter by Cuzon Carlson emphasizes the

striatum as a brain area where alcohol alters the excitatory and inhibitory balance of GABAergic and glutamatergic transmission. The contribution from Rossi and Richardson also emphasizes anatomical specificity, in this case recent data implicating the cerebellum as a site for alcohol's abuse liability through effects on $GABA_A$ channels. Next, the chapter by Hopf and Mangieri focuses on AMPA glutamate receptor (AMPAR)-mediated effects of alcohol, where advances in selective antagonists have helped illuminate subunit-specific aspects of ethanol sensitivity. Finally, another ionotropic receptor system that is prominent in the abuse aspects of alcohol is the nicotinic acetylcholine receptors. The chapter by Klenowski and Tapper provides an excellent overview of separate and common targets of alcohol and nicotine, particularly in the mesolimbic pathways with an emphasis on the apparent synergistic effects leading to comorbid addiction.

We selected two monoaminergic systems to highlight in this volume. The dopaminergic system has long occupied a predominant place in neuropharmacological aspects of addictive drugs, including alcohol. In the review by Siciliano, Karkhanis, Holleran, Melchior, and Jones, dopaminergic mechanisms that are determined under similar experimental conditions and translate across species are emphasized as a way of disentangling a complex literature. In addition to dopamine, the monoamine norepinephrine (NE) is also implicated in alcohol reinforcement mechanisms, particularly in relation to arousal, emotional regulation, and stress processes. The review by Vazey, den Hartog, and Moorman emphasizes recent findings and provides new directions for better understanding how the NE system is maladaptively altered by alcohol.

The interaction of alcohol and voltage-dependent ion channels is represented by one review on calcium channels and two reviews on potassium channels. As with the GABA and glutamate systems, alcohol research has a relatively long history with voltage-sensitive calcium channels, particularly with neurophysiological disturbances such as tremors and seizures. The review by N'Gouemo takes this complex subject and emphasizes the role of neuronal homeostasis and its disruption by chronic alcohol exposure. The large conductance voltage- and calcium-dependent potassium channel (BK) and channel interactions with alcohol are reviewed by Dopico, Bukiya, and Bettinger, with an emphasis on adaptations underlying tolerance to alcohol. Comparatively new to the neuropharmacology of alcohol is disruptions in intrinsic neuronal excitability by alcohol-induced adaptations in small-conductance calcium-activated (SK), voltage-dependent, and G-protein-activated inwardly rectifying potassium channels. These potassium channel mechanisms related to alcohol and impaired neuronal firing are reviewed elegantly by Cannady, Rinker, Nimitvilai, Woodward, and Mulholland.

The aspect of alcohol's pharmacology that is receiving renewed attention is alcohol-induced neuroinflammation involving immune signaling molecules. For this subject, we have included three reviews. The first review by Kim, McCullough, Poulson, Sanz-Garcia, Sheehan, Stravitsky, and Nagy provides the important perspective of how alcohol interferes with the hepatic immune system. The second review by Coleman and Crews focuses on innate immune signals as modulators of neurocircuitry involved in the addiction to alcohol and possibilities for new

treatment approaches. This is followed by a review from Roberto, Patel, and Bajo on the effects of key cytokines on molecular properties and synaptic transmission, particularly in the extended amygdala and hippocampus. From this collection of reviews, it is clear that targets and pharmacotherapies that emerge from the cancer biology field can be repurposed to address widespread organ dysfunction, including neuroinflammation, associated with heavy alcohol drinking.

The final set of reviews on neuropharmacological mechanisms of alcohol includes a review by Schreiber and Gilpin on the extended amygdala and corticotropin-releasing factor as a basic allosteric mechanism propagating excessive drinking. This is followed by a review of alcohol's interaction with dynorphin and orexin neuropeptide systems by Anderson, Moorman, and Becker. These two systems are closely interrelated and underlie homeostatic mechanisms that likely become dysfunctional under chronic alcohol exposure, leading to changes in motivational states that increase further alcohol consumption. The final mechanistic review is by Savarese and Lasek on genomic factors induced by alcohol that can change signal transduction mechanism and gene expression integral to long-term adaptations in chronic alcohol drinking. The emergence of new pharmacological agents that target transcriptional factors promises new directions in alcohol pharmacotherapy.

We conclude this volume with highly informative, comprehensive, and timely reviews on the practical side of alcohol neuropharmacology: approaches and outcomes of preclinical and human clinical studies of alcohol pharmacotherapeutics. The review by Egli provides background on the role of animal models as sensitive and efficient for rapid screening, but emphasizes that better translational approaches are needed to have potential pharmacotherapies retain efficacy in the arena of human outpatient treatment. The final review, by Litten, Falk, Ryan, Fertig, and Leggio, provides a history and current emphasis on developing efficacious and safe compounds for treating alcohol use disorder.

We sincerely believe that this volume provides a valuable and instructive view on the state of the art in our understanding of the depth and breadth of past, present, and future neuropharmacological research on alcohol. It remains a wonder that this simple 2-carbon alcohol can result in such complex neuropharmacology. There is no doubt that as we learn more about receptor systems, their circuitry, co-modulation, adaptive capacities, and underlying functions, we will learn more about the complex processes that result in alcohol use disorders. We hope you find this volume helpful in defining important directions of this exciting research.

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Contents