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Editors

Behavioral Pharmacology of the Cholinergic System

Springer

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Preface

The focus of this CTBN volume aims to provide an overview of cholinergic systems in relation to their effects on behavior and disease. Our intent was to organize a broad series of reviews that summarizes the past and current knowledge of cholinergic systems with in-depth discussions on the potential opportunities for harnessing this information for therapeutic development across central nervous system (CNS) disorders. This volume contains a collection of multidisciplinary chapters authored by leading experts who have made significant contributions in the field.

Research on cholinergic neurotransmission has revealed the diversity of behaviors this system modulates, including cognitive processes, pain, dependence, and addiction, among others. Dysfunction of the cholinergic system underlies nicotine addiction and has been implicated in various neurological and psychiatric disorders including dementia, pain, and Alzheimer's disease. The molecular genetics of the cholinergic system including both muscarinic and nicotinic acetylcholine receptors, cholinesterases, acetylcholine synthesis and release have provided significant insights into potential targets for pharmacological intervention. Cholinergic drugs are being used and are being evaluated for the treatment of many CNS diseases. Thus, this volume aims to broaden our understanding of the current state of cholinergic mechanisms to enable the implementation of novel approaches for the development of more effective treatments.

Acetylcholine (ACh), identified as a key neurotransmitter, has been observed to exert multiple effects on physiological functions which has paved the way toward the identification and characterization of two distinct receptor subtypes: nicotinic (nAChR) and muscarinic receptors (mAChR). In both cases, the effects of naturally occurring drugs acting on nAChRs and mAChRs have been exploited for both therapeutic and nontherapeutic purposes for hundreds of years, well before these receptors were identified. The first review presented by Bertrand and Wallace in the chapter "A Review of the Cholinergic System and Therapeutic Approaches to Treat Brain Disorders" will act as a foundational chapter to introduce cholinergic neurobiology and provides an in-depth discussion on the nAChR and mAChR receptors

systems, their function and the opportunity that targeting these systems provide for novel medications across disorders. The reader will note that several authors introduce the cholinergic receptor systems throughout the book for the purposes of their individual discussions, and this is the strength of the book in that each chapter can stand on its own, as well as contributes to the broader vision of the book.

Following the introduction, we evaluate cholinergic contributions to cognitive function including sensory perception and attention, memory and working memory processes from *ex vivo* preparations through rodents, nonhuman primates, and human behaviors. In the chapter “Acetylcholine and Spontaneous Recognition Memory in Rodents and Primates,” Easton, Barros, and Lever assess the impact of cholinergic manipulations on memory and highlight important considerations of what is meant by memory and how it is being modeled. In particular, they focus on the issue of translation from animal research into the clinic which is a key concern and argue that it is essential to move away from considering the debate to be one of ACh involvement in broadly described terms of “memory” or “attention,” but instead argue that one needs to look carefully at the precise nature of the behavioral task being used and the nature of the behavioral impairment. Specific hypotheses about the nature of acetylcholine’s function can be best arrived at through the careful consideration of specific elements of behavior and its relation to the manipulation at hand.

In the chapter “Endogenous Acetylcholine and Its Modulation of Cortical Microcircuits to Enhance Cognition,” Venkatesan, Jeoung, Chen, Power, Liu, and Lambe discuss the role of ACh in shaping sensory perception and attentional processes using electrophysiological and optogenetic methods to elucidate how and where ACh acts within the cortex to help shape cognitive processing and open the door to new approaches for identifying novel treatments for the perceptual and attention deficits found in multiple psychiatric and neurological disorders. Parikh and Bangasser expand on our understanding of the cholinergic mechanisms of attention highlighting the recent developments in the chapter “Cholinergic Signaling Dynamics and Cognitive Control of Attention.” Specifically, the evidence that phasic cholinergic signaling in the prefrontal cortex (PFC) is a causal mediator of signal detection is discussed. Moreover, studies that support the tonic neuromodulatory role of cholinergic inputs in top-down attentional control, and those that provide insights into the potential cellular substrates that integrate the phasic and neuromodulatory cholinergic signaling modes, are reviewed. The authors also incorporate considerations of sex differences that exist in the central cholinergic-attention system.

In the chapter “Involvement of Nicotinic Receptors in Working Memory Function,” Galvin, Arnsten, and Wang provide an in-depth discussion of the cholinergic system in the prefrontal cortex on working memory functions in nonhuman primates. The authors highlight how the dorsolateral prefrontal cortex is particularly critical for rule representation and working memory, or the ability to hold information “in mind” in the absence of sensory input, and present the emerging evidence that

supports a prominent and permissive role for ACh in these excitatory circuits, through actions at cholinergic nAChRs.

In the chapter “Nicotinic Receptors Underlying Nicotine Dependence: Evidence from Transgenic Mouse Models,” we move away from the involvement of the cholinergic system in cognitive processes and begin the discussion on the role of this system in dependence and addiction. Gipson and Fowler provide an elegant discussion on the contributions from transgenic mouse models that have added to our understanding of nicotine’s effects on the reward-related mesolimbic pathway and the aversion-related habenulo-interpeduncular pathway. Following in the chapter “Cholinergic Receptors and Addiction,” Papke, Brunzell, and De Biasi review the structure and diversity of nAChR subunits and how different nAChR subtypes play specific roles in the phenomenon of nicotine addiction. The authors also provide a compelling discussion on how brain cholinergic receptors are involved with areca addiction and the unique challenges for dealing with addiction to this substance, which is a major public health issue across most of South Asia.

In the chapter “Behavioral and Molecular Basis of Cholinergic Modulation of Pain: Focus on Nicotinic Acetylcholine Receptors,” Damaj and colleagues focus their review on the recent progress in our understanding of the cholinergic system as a target for pain modulation. In particular, they focus on nAChR subunit biology and balance the data supporting the therapeutic potential for this system in chronic pain with the inherent complexities associated with drug development in this space.

Chapter “An Evolving Therapeutic Rationale for Targeting the $\alpha 7$ Nicotinic Acetylcholine Receptor in Autism Spectrum Disorder” provides a comprehensive evaluation of the involvement of the cholinergic system in autism spectrum disorder (ASD). Deutsch and Burket review historic and recent literature supporting selective therapeutic targeting of the $\alpha 7$ nAChR in persons affected with ASD and summarize evolving literature that support the therapeutic exploration of selectively targeted cholinergic interventions for the treatment of ASD.

The discussion of therapeutic development for the cholinergic system continues in the chapter “Activators of $\alpha 7$ nAChR as Potential Therapeutics for Cognitive Impairment” by Wang, Bell, and Uslaner, who present rationale to support the $\alpha 7$ nAChR as a promising target for the treatment of cognitive deficits associated with psychiatric and neurological disorders, including schizophrenia and Alzheimer’s disease (AD). The authors highlight the progression of several compounds targeting the $\alpha 7$ nAChR, including agonists and positive allosteric modulators (PAMs) into early clinical trials and highlight none of the $\alpha 7$ nAChR ligands has been approved for clinical use. The chapter focuses on ligands that have advanced to clinical studies and provides an excellent overview that allows us to explore the reasons why these agents have not met with unequivocal clinical success.

The intent of this book is to maximize the reader’s insight into the translational perspective on targeting nicotinic and muscarinic acetylcholine receptors and to provide insight into the diverse array of disease states affected by dysfunction of

cholinergic systems. In summary, we aim for this volume to be thought-provoking and to continue the discussions and important research and development efforts into the cholinergic system for treating diseases of the central nervous system.

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