
Preface

Nicotinic acetylcholine receptors (nAChRs) are neuron proteins that signal muscular contraction in response to a chemical stimulus. They are cholinergic receptors that form ligand-gated ion channels in the plasma membranes of certain neurons and on the presynaptic and postsynaptic sides of the neuromuscular junction. One of the best-studied ionotropic receptors, nAChRs are linked directly to ion channels and do not use second messengers as metabotropic receptors do.

To date, 17 nAChR subunits have been identified, which can be divided into muscle type and neuronal type. Of these subunits, $\alpha 2$ – $\alpha 7$ and $\beta 2$ – $\beta 4$ were identified in humans; the remainders were discovered in chick and rat genomes.

The nAChR subunits belong to a multigene family, and the assembly of combinations of subunits results in a large number of receptors. These receptors, with highly variable kinetic, electrophysiological, and pharmacologic properties, respond to nicotine differently at very different effective concentrations. This functional diversity allows nAChRs to take part in two major types of neurotransmission. Classical synaptic (i.e., wiring) transmission involves the release of high concentrations of a neurotransmitter that act on immediately neighboring receptors. In contrast, paracrine (i.e., volume) transmission involves neurotransmitters released by synaptic buttons, which then diffuse through the extracellular medium until they reach their receptors, which may be distant. Nicotinic receptors also can be found in different synaptic locations; for example, the muscle receptor always functions postsynaptically. The neuronal forms of the receptor can be found both postsynaptically (involved in classical neurotransmission) and presynaptically, where they can influence the release of multiple neurotransmitters.

Because nAChR subunits are one of the largest and most complex receptor families, numerous studies have been conducted on them in many organisms. These studies documented clearly that nAChRs are involved in a wide range of neuronal activities, including cognitive functions, neuronal development, and neuronal degeneration. Because of the broad distribution of nAChRs in various brain regions and the many types of receptors formed by different combination of nAChR subunits, this receptor family has been indicated to play important roles in many psychiatric diseases, such as Alzheimer's disease, depression, schizophrenia, addiction, and ingestive behaviors. Importantly, many agonists and antagonists have been developed for potential treatment of various diseases. For example, varenicline (Chantix), an $\alpha 4\beta 2$ -nAChR partial agonist, has been approved by the U.S. Food and Drug Administration to treat smoking addiction. Recently, there has been evidence that it may be effective in treating alcoholism as well. In addition, agonists or antagonists of various specific nAChRs have been suggested for the treatment of Alzheimer's disease as well as depression.

To understand the biochemistry and function of nAChRs, numerous biochemical and molecular techniques have been developed for different organisms and experimental systems. The primary goal of this book is to provide not only updated knowledge about the properties and biological function of various types of nAChRs but also the methods and approaches for manipulating them in different organisms. To reach this goal, a group of

esteemed scientists who have been engaged in research on nAChRs with different approaches and organisms was invited to contribute. The first chapter, by Ackerman and Boyd, provides a detailed description of the molecular techniques commonly used to study the expression of nAChR subunits as well as their identification and characterization in zebrafish. The second and third chapters describe several behavioral tests used to investigate nicotinic drugs to obtain knowledge of reinforcement, learning, and memory, again using zebrafish as the animal model. The fourth chapter, authored by Fuenzalida-Urbe and colleagues, discusses some methodological approaches, with special emphasis on chronoamperometry, that have been used to elucidate the contribution of nicotinic ligands to the regulation of aminergic signaling in the *Drosophila* brain. In Chap. 5, Philbrook and Francis describe emerging technologies and methods for the analysis of *C. elegans* nAChRs with an emphasis on strategies for identifying and characterizing genes involved in the biological regulation of the nervous system. In Chap. 6, Wilking and Stitzel provide an update of their investigation of a naturally occurring single nucleotide polymorphism (SNP) in the mouse nAChR $\alpha 4$ subunit gene, *Chrna4*, that leads to an alanine/threonine change in the sequence at amino acid position 529. By generating a knockin mouse strain, the authors showed that the *Chrna4* T529A polymorphism affects both nAChR function and nicotine-induced behaviors. In Chap. 7, Fox-Loe and colleagues introduce several cutting-edge fluorescence techniques used to pinpoint distinct changes in the location, assembly, export, vesicle trafficking, and stoichiometry of nAChRs. In Chap. 8, Nashmi provides a detailed description of the spectral confocal imaging procedure used to optimize the imaging and quantification of the $\alpha 4$ -nAChR subunit fused to yellow fluorescent protein, from fixation to imaging and spectral unmixing. Chapter 9, authored by Oz and colleagues, and Chap. 10, by Lorke and colleagues, provide comprehensive reviews of the rationales and progress for using various allosteric modulators of $\alpha 7$ -nAChRs as novel agents for treating Alzheimer's disease. Similarly, in Chap. 11, Zhang and colleagues discuss various compounds developed by targeting $\alpha 4\beta 2$ -nAChRs for the treatment of depression. Finally, in Chap. 12, Li and colleagues describe a comprehensive evolutionary relation of most, if not all, nAChR subunits in both vertebrate and invertebrate species.

Together, these chapters provide a broad view of recent advances in nAChR research in different species and various fields. It is our hope that the book can provide readers with a greater understanding of these new developments, especially the technology aspects. I am most grateful to the distinguished researchers who have come together to produce this important and valuable book. These experts, united in their mission to deliver a scholarly and comprehensive book, come from both animal and human research fields. I am grateful for all that they taught me through their contributions and for the knowledge they will convey to all who read this book.

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<http://www.springer.com/978-1-4939-3766-0>

Nicotinic Acetylcholine Receptor Technologies

Li, M. (Ed.)

2016, XII, 259 p. 23 illus., Hardcover

ISBN: 978-1-4939-3766-0

A product of Humana Press