

Preface

Understanding of nicotinic acetylcholine receptors

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Cigarette smoking is a major public health problem and has been identified as the second-most prevalent cause of death in the world. China, a country with a population of 1.3 billion, is the world's largest producer and consumer of tobacco. It estimates that there are 0.35 billion cigarette smokers in China, which bears a large proportion of the deaths attributable to smoking worldwide^[1]. Cigarette smoking results in more than 1 000 000 premature deaths each year in China — about 1 in every 5 premature deaths^[2]. Economically, more than \$166 billion per year of total Chinese healthcare costs are attributable directly to smoking-associated diseases. If the costs of lost productivity due to smoking are added (estimated at \$86 billion per year), the economic burden of smoking is more than \$252 billion per year, in China alone. Recent estimates indicate that approximately one-quarter of the world's population smokes, that smoking is currently responsible for 1 in every 10 premature deaths worldwide (about 5 million deaths each year)^[3], and that this number will double by 2025 unless effective action is taken. Thus, there is an urgent need to reduce smoking prevalence worldwide. Unfortunately, nicotine dependence severely confounds attempts to end tobacco product use.

Nicotine is the major biologically active substance that promotes the use of tobacco products. Nicotine exerts its biological effects through nicotinic acetylcholine receptors (nAChRs). nAChRs are prototypical members of the ligand-gated ion channel superfamily of neurotransmitter receptors^[4]. nAChRs represent both classic and contemporary models for the establishment of concepts pertaining to mechanisms of

drug action, synaptic transmission, and structural/functional diversity of transmembrane signaling molecules^[4]. Neuronal nAChRs are found throughout the central nervous system and exist as multiple, diverse subtypes of pentameric structures with unique combinations from at least twelve ($\alpha 2$ – $\alpha 10$, $\beta 2$ – $\beta 4$) genetically-distinct subunits^[5]. Binding by endogenous (acetylcholine) or exogenous (nicotine) agonists to nAChR opens an intrinsic ion channel in the receptor, allowing the flow of cation ions (Na^+ , Ca^{2+} , and K^+) through the cell membrane, and inducing a wide variety of biological responses. Accumulating lines of evidence demonstrate that nAChRs play critical roles in mediating nicotine reward, dependence and addiction^[6, 7]. In addition, alterations of nAChRs have been found in various diseases such as Parkinson's diseases, Alzheimer's disease, schizophrenia, depression, epilepsy, diabetes, respiration disorders and some immunological disorders^[8]. Therefore, understanding the molecular biology, physiology, pharmacology and pathophysiology of neuronal nAChRs will significantly improve the diagnosis, prevention and treatment of these diseases and pathological conditions, including nicotine addiction.

Until recently, much of our understanding of the physiology and pharmacology of neuronal nAChRs has come from heterologous expression studies. Principally using *Xenopus* oocytes as hosts, but also using transfected mammalian cells, these efforts have helped to define the realm of possibilities for nAChR subunit combinations that can form functional channels^[9]. A variety of experimental approaches have been employed in the study of natively-expressed nAChRs, including molecular and cellular biology, electrophysiology, neurotransmitter release analyses, isotopic ion flux studies, immunochemistry, neuroanatomy, calcium imaging and behavioral testing. Studies using transgenic mice have helped to identify subunits that constitute some native, functional nAChR subtypes. Recently, significant insights have been

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gained regarding the molecular, cellular and system basis of nAChR function in the brain. For instance, at the atomic and molecular level, X-ray crystallographic structures of acetylcholine binding proteins (AChBPs) are providing new answers to questions about how nAChRs function as biophysical machines, and as participants in cellular and systems physiology^[10]. The studies of structure-function relationships have revealed that the structures of different nAChRs with different pharmacological profiles and kinetics will help to illustrate how agonists and antagonists bind to orthosteric binding sites, how allosteric modulators alter receptor function by binding outside these sites, how nAChRs gate ion flow, and how nAChR cytoplasmic domains affect receptor function^[4, 11, 12]. At the level of cellular and system biology, the functional subtypes of native nAChRs have been identified in different brain areas and their roles in the mediation of nicotine reward, dependence and addiction are beginning to be elucidated^[5, 13, 14]. Particularly, nicotine-induced neuronal adaptations (nAChR up-regulation and synaptic plasticity) in the brain reward center (ventral tegmental area) have been postulated as an important cellular mechanism of nicotine reinforcement^[15-17]. At the behavioral level, nicotine self-administration experiments combined with nAChR subunit knockout mice have provided important evidence concerning which nAChR subtypes are crucial for nicotine seeking behavior^[7, 18, 19]. Finally, based on the above experimental data, some theoretical models of nAChR-associated signal pathways and neuronal circuits have been proposed to interpret the roles of nAChRs in addiction, neurodegeneration, and mental illness^[20-22].

Collectively, multiple findings indicate that nAChRs in the brain play roles not only in the mediation of classical, excitatory, cholinergic neurotransmission at selected loci, but also, and perhaps more globally, in the modulation of neurotransmission by other chemical messengers, including glutamate, GABA, the monoamines, including dopamine, norepinephrine and serotonin, and acetylcholine (ACh) itself. This means that some nAChR subtypes have postsynaptic (or peri-synaptic), somatodendritic localizations, whereas others have pre-synaptic dispositions. Moreover, some nAChRs have been implicated in processes such as structuring and maintenance of neurites and synapses. Thus, nAChRs may play complex and important roles in neuronal function and in neurological and psychological diseases.

In this nAChR-themed issue, I bring together many of world's leading researchers in the nAChR research field to provide state-of-the-art reviews, and original research articles, covering a wide range of nAChR-related areas. These articles span from molecular to behavioral investigations

involving different experimental techniques such as molecular/cell biology, biophysics, electrophysiology, receptor pharmacology and behavioral testing. The articles in this specific issue provide a broad perspective on current advances in nAChR studies. I hope this issue will provide a foundation for future developments in nAChR research. In particular, I sincerely hope that this specific issue will promote the further engagement of Chinese scientists in nAChR-related research, smoking cessation efforts, and the management of smoking-associated diseases in China.

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