Current Topics

Functional Changes Induced by Long-Term Stimulation of Nicotinic Acetylcholine Receptors

Foreword

Akinori AKAIKE

*Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Kyoto University;
46-29 Yoshida-shimo-adachi-cho, Sakyo-ku, Kyoto 606-8901, Japan.*

Recent advances in studies of nicotinic acetylcholine receptor (nAChR) have led a better understanding of functions of receptor subtypes expressed in various organs including the central nervous system (CNS), the autonomic nervous system, endplate of the skeletal muscle, the cardiovascular system and the immune system. nAChRs are the typical ligand-gated ion channels that evoke cation-selective currents across the plasma membrane. They are composed of pentameric composition of distinct subunits. Distinct functional properties of the receptor subtypes are attributed to the different association of subunits. The subtypes of nAChR are classified on the basis of the predominant α -subunits ($\alpha 1$ to $\alpha 10$) as agonists including acetylcholine (ACh) and nicotine are known to bind α -subunits to trigger receptor activation. $\alpha 1$ nAChR is expressed in the skeletal muscle and is composed of two kinds of subtype combinations; ($\alpha 1$)₂ $\beta 1\gamma\delta$ (embryonic) and ($\alpha 1$)₂ $\beta 1\epsilon\delta$ (adult). Neuronal nAChRs are formed from the combination of α - and β -subunits. Among those neuronal receptors, $\alpha 3$ nAChR is highly expressed in the autonomic ganglion though this subtype is also expressed in CNS. The most predominant subtypes of nAChRs expressed in CNS are $\alpha 4$ (also known as $\alpha 4\beta 2$) and $\alpha 7$ nAChRs. The neuronal nAChRs mediate fast synaptic transmission in the autonomic ganglions and CNS. nAChRs in CNS also play an important role in the regulation of neurotransmitter release in the various regions including the stratum, the hippocampus and the cerebral cortex. Accumulating evidence also reveals the expression of some nAChR subtypes such as $\alpha 7$ in the immune cells and glial cells though the functions of those receptors are yet to be determined.

On exposure to the agonists, nAChR exerts an active, open state and elicits rapid depolarization. Thus, nAChR are classified as an excitatory receptor, which evokes rapid excitation in neuronal, muscular and secreting cells. The progressive decline of the agonist-evoked current reveals the closure of the channel and nAChR exerts a desensitized, non functional states. Moreover, it has been widely recognized that nAChRs mediate the long-term modification of cell functions *via* specific signaling systems as well as the short-term excitation of the cells. nAChRs generate specific and complex Ca^{2+} signals that include adenylyl cyclase, protein kinase A, protein kinase C (PKC), Ca^{2+} -calmodulin-dependent kinase and

phosphatidylinositol 3-kinase. These phosphorylated downstream targets cellular signaling related to exocytosis, extracellular signal-regulated mitogen-activated protein kinase (ERK)-linked neuronal functions such as memory, addiction, and cell survival and development.

nAChRs are also recognized as major molecules mediating pharmacological action of tobacco smoking. Nicotine is a major ingredient of tobacco and stimulates all of the subtypes of nicotinic receptors like ACh though nicotine induces rapid desensitization of the most nAChRs. Interestingly, long-term tobacco smoking or nicotine application induces up-regulation of nAChRs and, in most cases, facilitates their functions. This phenomenon is quite unique as the persistent receptor stimulation by specific agonists induces down-regulation of receptors and reduction of receptor functions in most of the receptors expressed in the nervous system, including muscarinic receptors, another major subtype of cholinergic receptors. Receptor up-regulation following long-term exposure to nicotine may be linked with the diverse properties of nAChRs from the enhancement of learning and memory to addiction and neuroprotection although the precise mechanisms of the up-regulation are not fully understood.

This mini-review series aims to introduce recent advances on research of the longer-lasting effects generated by activation of nAChRs. The authors are members of the project research for functional changes induced by long-term stimulation of nAChRs, supported by Smoking Research Foundation, Japan. Persistent stimulation of nAChRs occurs during habitual tobacco smoking as well as cholinesterase inhibitor therapy for Alzheimer's disease. Long-term exposure of receptors to nAChR agonists or cholinesterase inhibitors contribute to the elaboration of complex intracellular signals, resulting functional changes of the cells expressing nAChRs in CNS, the cardiovascular system and the immune system. Functions and regulating mechanisms of nAChRs themselves are also modified during the course of receptor up-regulation. The concept that nAChRs are ligand-gated ion channels that generate fast electrical signals will be supplemented with more complex mechanisms in which nAChRs are important elements triggering complex cell signaling toward the gradual alteration of cellular functions.