Journal of Biochemistry and Cell Biology

Muscle and Neuronal Nicotinic Acetylcholine Receptors

Socrates J Tzartos*

Department of Pharmacy, University of Patras, GR26500, Rio Patras, Greece

Editorial

Nicotinic acetylcholine receptors (nAChRs) are integral membrane proteins and prototypic members of the ligand-gated ion-channel superfamily, which has precursors in the prokaryotic world. They are formed by the assembly of five transmembrane subunits, selected from a pool of 17 homologous polypeptides (α1–10, β1–4, γ, δ, and ε). There are many nAChR subtypes, each consisting of a specific combination of subunits, which mediate diverse physiological functions. They are widely expressed in the central nervous system, while, in the periphery, they mediate synaptic transmission at the neuromuscular junction and ganglia. nAChRs are also found in non-neuronal/nonmuscle cells (keratinocytes, epithelia, macrophages, etc.). Extensive research has determined the specific function of several nAChR subtypes. nAChRs are now important therapeutic targets for various diseases, including myasthenia gravis, Alzheimer's and Parkinson's diseases, and schizophrenia, as well as for the cessation of smoking. However, knowledge is still incomplete, largely because of a lack of high-resolution X-ray structures for these molecules. Nevertheless, electron microscopy studies on 2D crystals of nAChR from fish electric organs and the determination of the high-resolution X-ray structure of the acetylcholine binding protein (AChBP) from snails, a homolog of the extracellular domain of the nAChR, have been major steps forward and the data obtained have important implications for the design of subtype-specific drugs. Here, we review some of the latest advances in our understanding of nAChRs and their involvement in physiology and pathology.

Exposure to cigarette smoke, either by active smoking or second-hand smoke, is the main cause of lung cancer. In addition, about one-third of all lung cancer patients continue to smoke after diagnosis [1]. Nicotine is a major component of cigarette smoke, but the role of nicotine in carcinogenesis and response to cancer treatment is not well understood. Nicotine is well known for its activity in the brain. The receptor for nicotine, the nicotinic acetylcholine receptor (nAChR), is responsible for mediating effects in mood in the brain during and after nicotine exposure. The nAChR are pentamers composed of specific combinations of nAChR subunits that form functional receptors. Specifically, the muscle type nAChR consists of the **α**1/**β**1/**δ**/**ε** subunits, with the **β**1 subunit occurring twice to form the pentamer [2]. The other major nAChR types are the neuronal heteropentamers, consisting of three **α** subunits (**α**2–**α**6) and two **β** subunits (**β**2–4), and the neuronal homopentamers, which are pentamers of the same subunit, most frequently **α**7. Other nAChR combinations are possible that contain the novel **α**- subunits **α**9 and **α**10, but they have not been characterized as thoroughly. In addition, nicotine appears to act as an antagonist of the **α**9 and **α**10 receptors, instead of an agonist.

We have recently characterized the mRNA and protein for nAChR subunits present in normal human bronchial epithelial (HBE) cells. These cells have saturable nicotine binding sites, and upon exposure to nicotine, lead to phosphorylation of the signaling protein p38^{MAPK} (MAPK – mitogen-activated protein kinase) and Akt [3]. In addition, it has also been shown that nicotine leads to an increase in proliferation in some non-neuronal cell cultures, including small cell lung cancer cell lines. These and other data suggest that nicotine may act as a tumor promoter in the airway. The nAChR subunits expressed by non-small cell lung cancer (NSCLC) cells at the mRNA level has not been compared to the expression of protein in these cells, nor have they been examined for expression on the cell membrane. Our previous studies in HBE cells, as well as other published studies in neurons, have shown that nAChR mRNA expression does not necessarily correlate with protein expression or expression of functional nicotinic receptor on the cell membrane. Furthermore, the functionality of nAChR in NSCLC cell lines has not been established [4].

In the work reported here, we determined the types of nAChR that are expressed as mRNA and protein in human NSCLC cell lines [5], and the expression of receptors on the surface of tumor cells within human NSCLC tissues. In addition, we determined the functionality of these receptors, and their ability to initiate signaling consistent with that of a regulator of cell proliferation and survival. Furthermore, we determined the ability of nicotine to protect NSCLC cells from the effect of the EGFR tyrosine kinase inhibitor gefitnib, an approved therapy for NSCLC [6].

Addiction to nicotine is the underlying reason why many people continue to smoke tobacco. Studies show that most adult smokers express the desire to quit smoking but are unable, and many try to quit without success [7]. This remains true even after diagnosis of lung cancer. Among patients who are active smokers at the time of diagnosis, 30% continued to smoke. In addition, 5% of lung cancer patients who were former smokers at diagnosis relapse and begin smoking again after diagnosis [8].

Acknowledgment

Conflicts of Interest

The author has no known conflicts of interested associated with this paper.

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*Corresponding author: Socrates J Tzartos, Department of Pharmacy, University of Patras, Rio Patras, Greece, E-mail: tzartos@upatras.gr

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