Chapter 10
Neuronal Nicotinic Acetylcholine Receptor Expression and Function on Nonneuronal Cells

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Abstract Of the thousands of proven carcinogens and toxic agents contained within a cigarette, nicotine, while being the addictive agent, is often viewed as the least harmful of these compounds. Nicotine is a lipophilic molecule whose effects on neuronal nicotinic acetylcholine receptors (nAChR) have been primarily focused on its physiologic impact within the confines of the brain and peripheral nervous system. However, recently, many studies have found neuronal nAChRs to be expressed on many different nonneuronal cell types throughout the body, where increasing evidence suggests they have important roles in determining the consequences of nicotine use on multiple organs systems and diseases as diverse as ulcerative colitis, chronic pulmonary obstructive disease, and diabetes, as well as the neurologic disorders of Parkinson’s and Alzheimer’s disease. This review highlights current evidence for the expression of peripheral nAChRs in cells other than neurons and how they participate in fundamental processes, such as inflammation. Understanding these processes may offer novel therapeutic strategies to approach inflammatory diseases, as well as precautions in the design of interventional drugs.

Keywords nicotine, inflammation, nicotinic receptors, nonneuronal

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Introduction

Neuronal nicotinic acetylcholine receptors (nAChR) are ligand-gated ion channels whose genetics and functional properties have been studied largely for their role in modulating neurotransmission. This receptor system has also been recognized as a participant in the progression of severe pathologies of the brain. For example, the high affinity nicotine receptors are among the first (if not the first) neurotransmitter system whose expression is diminished in Alzheimer’s disease. Subsequent studies have suggested that chronic nicotine administration might in fact play a beneficial role in slowing the progression of this disease. While this finding is controversial, there is now ample evidence supporting a therapeutic benefit from nicotine in Parkinson’s disease, and as a neuroprotectant to toxic insults such as excitotoxins or Beta-amyloid derived peptides. Understanding the mechanistic basis for these and other similarly interesting findings, including a cognitive benefit from nicotine, would be of obvious importance. The name “neuronal” was based principally on the tissue source of the DNA libraries from which these receptors were first cloned, the brain, but growing evidence indicates that cells other than neurons throughout the body express these receptors including lymphocytes, macrophages, dendritic cells, adipocytes, keratinocytes, endothelial cells, and epithelial cells of the intestine and lung. This extended expression of nAChRs is of importance because, in addition to their regulation by endogenous agonists such as acetylcholine, choline, and the exogenous compound nicotine, their impact upon peripheral processes can be quite diverse as exemplified by their ability to in some cases enhance (Crohn’s disease) disease or in other cases diminish (ulcerative colitis) progression. These apparent contradictions in the effects of nicotine are not uncommon and understanding this complex biology will in turn optimize therapeutic benefit to ensure that neuroprotective therapy for one disease does not promote immune dysfunction and the survival of unwanted cells in other tissues.

Acetylcholine Receptors

Acetylcholine receptors (see Lindstrom and Hogg et al) consist of 2 major subtypes, the muscarinic-activated metabotropic receptors (second messenger coupled) and the fast-ionotropic cationic nicotine-activated channel receptors, both of which are activated by the endogenous neurotransmitter, acetylcholine. Receptors of the nicotinic subclass can be distinguished further as “muscle” or “neuronal.” While the muscle and neuronal nicotinic receptors exhibit similar sensitivity to gating by acetylcholine, the muscle receptor is much less sensitive to nicotine. Hence, at physiological concentrations, the majority of nicotine’s effects are through neuronal nicotinic acetylcholine receptors (nAChR), and, in fact, when nicotine levels are sufficiently high to act upon the muscle receptor (as might occur when smokers concurrently use the transdermal nicotine patch), difficulties in breathing and muscle spasms that can result in death may occur.