Paying Attention to Your Acetylcholine, Part 2

The Function of Nicotinic Receptors

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Issue: The many types of nicotinic cholinergic receptors differ in their structure, function, location, response to drugs, and involvement in cognitive disorders such as Alzheimer’s disease and schizophrenia.

In this second part of a 2-part series, we present the role of nicotinic cholinergic receptors in regulating neurotransmission and in mediating cognitive functions in health and disease. Last month, we discussed the structure of nicotinic cholinergic receptors.1

Nicotinic Receptor Molecular Subtypes

Nicotinic receptors have an ever-increasing array of subtypes defined by which 5 of the many possible subunits are grouped together.1–3 Some of the best known examples and their hypothetical functions are shown in Figures 1 and 2. For example, outside the brain, unique nicotinic receptors are located postsynaptically in skeletal muscle where they mediate contraction of skeletal muscle.2,3 Other types of nicotinic receptors are located in the autonomic ganglia of the peripheral nervous system where they regulate the autonomic nervous system.2,3

In the brain, there are many subtypes of nicotinic receptors, and 2 of the most important are shown in Figures 3 and 4. The $\alpha_4\beta_2$ subtype may be involved postsynaptically in excitatory neurotransmission. More of these receptors may be lost early in Alzheimer’s disease than other nicotinic receptor subtypes.5 The $\alpha_7$ subtype is predominantly presynaptic6 and is located not only on cholinergic terminals, but also on the terminals of numerous noncholinergic neurons.1 These presynaptic $\alpha_7$ nicotinic receptors are responsible for generating very fast calcium currents and, when they do so, causing neurotransmitter release. Thus, $\alpha_7$ nicotinic receptors enhance not only acetylcholine release, but also the release of glutamate, serotonin, and other neurotransmitters.7 In addition, they may mediate dopamine release in response to nicotine, particularly in the nucleus accumbens, thereby activating the classic “reward” pathway and causing addiction to cigarettes.8

Nicotinic Receptor Pharmacologic Subtypes

Since the molecular configurations of nicotinic receptors differ in various sites of the body and in various sites within the brain, it is theo-
nically possible that therapeutic agents could be found that would act at nicotinic receptors at some sites but not at others. If so, this might allow desirable CNS-mediated cognitive actions without undesirable peripherally mediated side effects. Although some drugs bind more readily to certain nicotinic receptors than to others, this pharmacologic binding affinity does not necessarily correlate specifically with molecular configurations.

**Nicotinic Receptors and Cognition**

Nicotinic agonists improve attention in normal people and may improve cognitive function in patients with Alzheimer’s disease. The α7 nicotinic receptors may inhibit β-amyloid–induced neuronal death and thereby confer a neuroprotective action in Alzheimer’s disease. In addition, strong genetic and pharmacologic evidence suggests that the α7 nicotinic receptor is involved in the attentional and cognitive deficit associated with schizophrenia, known as an auditory-gating deficit. 


**REFERENCES**


**Take-Home Points**

- Different subtypes of nicotinic cholinergic receptors are formed when various subunits are assembled.
- Presynaptic α7 nicotinic receptors regulate not only acetylcholine release, but also the release of other neurotransmitters, such as glutamate, serotonin, and dopamine.
- The α7 nicotinic receptors may mediate the ability of nicotine to enhance attention and to cause addiction to smoking.
- The α7 nicotinic receptors may also be abnormal in schizophrenia, thus causing a cognitive problem signified by problems in sensory gating. These receptors may also be the ultimate target of drugs for Alzheimer’s disease that boost acetylcholine and improve memory and behavior.