

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 $\alpha_4\text{-}\beta_2$ subtype may be involved postsynaptically in excitatory neurotransmission.⁴ More of these receptors may be lost early in Alzheimer's disease than other nicotinic receptor subtypes.⁵ The α_7 subtype is predominantly presynaptic⁶ and is located not only on cholinergic terminals, but also on the terminals of numerous noncholinergic neurons.⁷ These presynaptic α_7 nicotinic receptors are responsible for generating very fast calcium currents and, when they do so, causing neurotransmitter release. Thus, α_7 nicotinic receptors enhance not only

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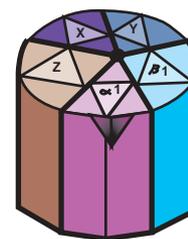
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Figure 1. $\alpha\beta\delta\gamma$



Location:
Neuromuscular junction.
Postsynaptic.
Function:
Contracts skeletal tissue

Figure 2. $\alpha\beta\text{XYZ}$



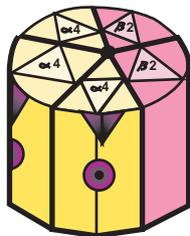
Location:
Peripheral nervous system
autonomic ganglia. Postsynaptic.
Function:
Regulates the autonomic nervous
system; releases catecholamines
from the adrenal gland.

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

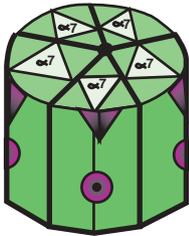
Since the molecular configurations of nicotinic receptors differ in various sites of the body and in various sites within the brain, it is theo-

Figure 3. $\alpha_4\beta_2$



Location: Central nervous system.
 Presynaptic or postsynaptic.
 Function: May be involved in neuronal migration during brain development; decreased in cerebral cortex in early Alzheimer's disease; up-regulated by nicotine for smoking.

Figure 4. α_7



Location: Central nervous system.
 Presynaptic.
 Function: Regulates a calcium channel; rapidly desensitizes after stimulation by agonists; stimulates further acetylcholine release; stimulates release of glutamate, serotonin, norepinephrine, and other neurotransmitters; regulates auditory-gating deficit of schizophrenic patients; is the target of novel cognitive enhancers.

retically possible that therapeutic agents could be found that would act at nicotinic receptors at some sites but not at others.² If so, this might allow desirable CNS-mediated cognitive actions without undesirable peripherally mediated side effects.^{2,3} 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.³

NICOTINIC RECEPTORS AND COGNITION

Nicotinic agonists improve attention in normal people and may improve cognitive function in patients with Alzheimer's disease.⁹ The α_7 nicotinic receptors may inhibit β -amyloid-induced neuronal death and thereby confer a neuroprotective action in Alzheimer's disease.¹⁰ In addition, strong genetic and pharmacologic evidence suggests that the α_7 nicotinic receptor is involved in the attentional and cognitive deficit associated with schizophrenia, known as an auditory-gating defi-

cit.¹¹ Agonists of the α_7 nicotinic receptor might reverse this dysfunction in schizophrenic patients, thereby improving cognition.

SUMMARY

Discoveries of the functions of nicotinic receptors are occurring at a fast pace. A great deal of attention is being directed to one specific receptor subtype, the α_7 nicotinic receptor, as a potential target for improving cognition in both Alzheimer's disease and schizophrenia. ♦

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Take-Home Points

- ♦ Different subtypes of nicotinic cholinergic receptors are formed when various subunits are assembled.
- ♦ Presynaptic α_7 nicotinic receptors regulate not only acetylcholine release, but also the release of other neurotransmitters, such as glutamate, serotonin, and dopamine.
- ♦ The α_7 nicotinic receptors may mediate the ability of nicotine to enhance attention and to cause addiction to smoking.
- ♦ The α_7 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.