Paying Attention to Your Acetylcholine, Part 2

The Function of Nicotinic Receptors

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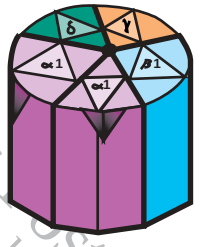
Issue: *The many types of nicotinic cholinergic receptors differ in their structure, function, location, response to drugs, and involvement in cognitive disorders such as Alzheimer's disease and schizophrenia.*

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

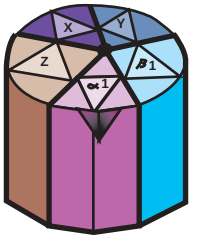
Nicotinic receptors have an ever-increasing array of subtypes defined by which 5 of the many possible subunits are grouped together.[1–3] Some of the best known examples and their hypothetical functions are shown in Figures 1 and 2. For example, outside the brain, unique nicotinic receptors are located 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]

Figure 1. αβδγ



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

Figure 2. αβXYZ



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

In the brain, there are many subtypes of nicotinic receptors, and 2 of the most important are shown in Figures 3 and 4. The α_4-β_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 presynaptic[6] 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 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-

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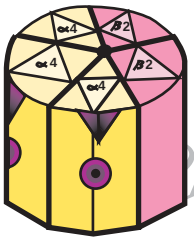
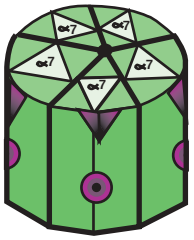
Figure 3. α_4-β_2



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 deficit.[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.