

The New Cholinesterase Inhibitors for Alzheimer's Disease, Part 2

Illustrating Their Mechanisms of Action

Stephen M. Stahl, M.D., Ph.D.

Issue: *Three new pharmacologic agents for the treatment of Alzheimer's disease all inhibit the enzyme acetylcholinesterase. These include donepezil (Aricept), rivastigmine (Exelon), and soon galantamine (Reminyl). Rivastigmine also inhibits the enzyme butyrylcholinesterase. Galantamine is also a selective booster of nicotinic action by allosterically modulating nicotinic receptors. These distinct pharmacologic profiles are potentially important to clinicians who must decide when to treat Alzheimer's disease and which cholinesterase inhibitors to use.*

In last month's BRAINSTORMS feature,¹ we discussed the distinctive pharmacologic mechanisms of action of 3 new acetylcholinesterase inhibitors, namely donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). Here we illustrate these properties.

REFERENCE

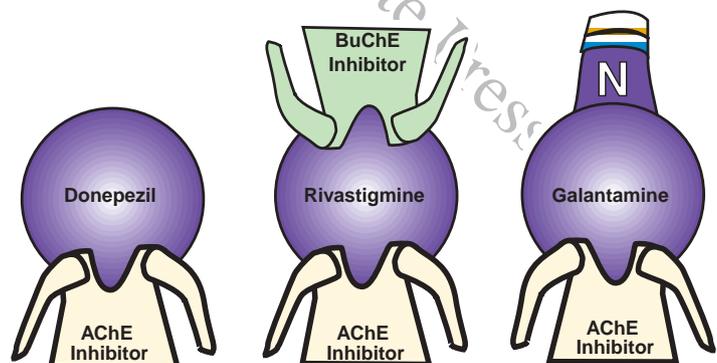
1. Stahl SM. New cholinesterase inhibitors for Alzheimer's disease, part 1: their similarities are different [BRAINSTORMS]. *J Clin Psychiatry* 2000;61:710-711

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From the Clinical Neuroscience Research Center in San Diego and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, 8899 University Center Lane, Suite 130, San Diego, CA 92122.

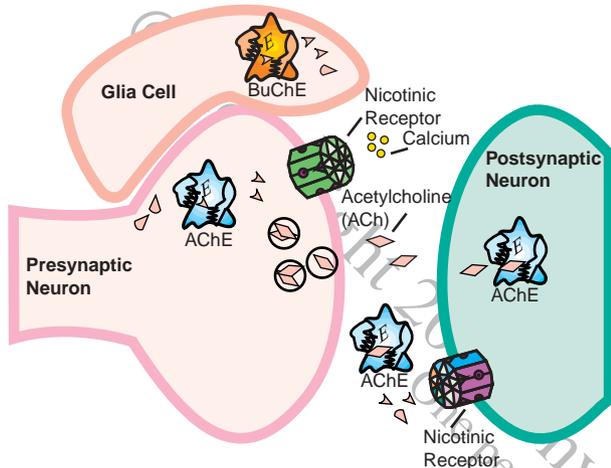
Figure 1.
Icons Representing 3 New Agents
for the Treatment of Alzheimer's Disease^a



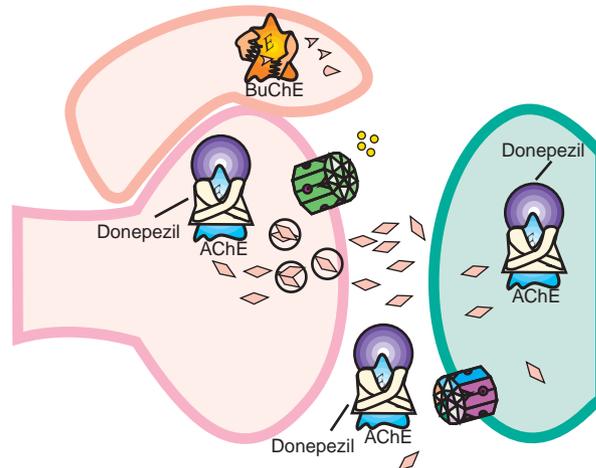
^aDonepezil (Aricept) is a selective inhibitor of acetylcholinesterase (AChE). Rivastigmine (Exelon) is a dual inhibitor of both AChE and butyrylcholinesterase (BuChE). Galantamine (Reminyl) not only is an inhibitor of AChE, but is also an allosteric modulator of central nicotinic receptors.

Figure 2.
Cholinergic Functioning and Mechanisms of Action^a

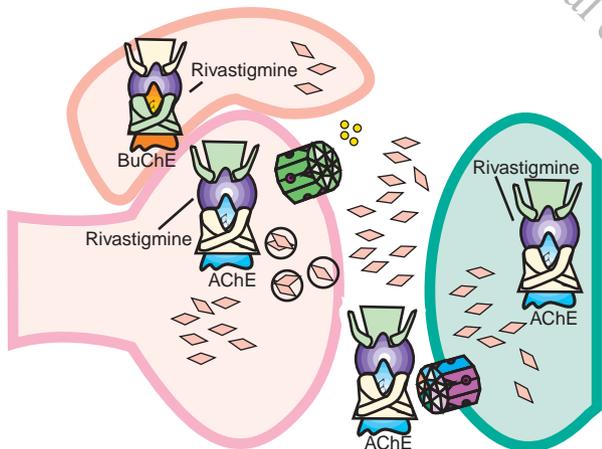
A: Normal Cholinergic Neuron Functioning



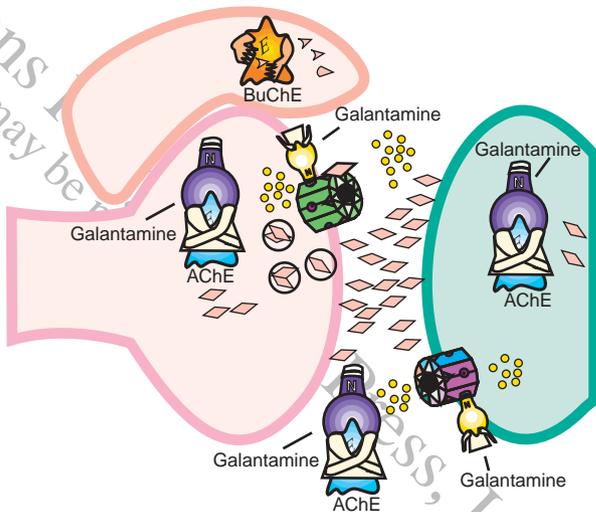
B: Mechanisms of Action of Donepezil



C: Mechanisms of Action of Rivastigmine



D: Mechanisms of Action of Galantamine



^aShown in these figures are the cholinergic neuron and the 3 targets (acetylcholinesterase [AChE], butyrylcholinesterase [BuChE], and nicotinic cholinergic receptors) of one or more of the new cholinesterase inhibitors. Normally, AChE breaks down the neurotransmitter acetylcholine (ACh) presynaptically (2A, left) and postsynaptically (2A, right), as well as extracellularly. Inhibition of AChE causes ACh levels to increase. All 3 cholinesterase inhibitors block this enzyme (2B–D). Donepezil blocks only AChE (2B), thus improving cognition and possibly helping to reduce disruptive behavior common to Alzheimer patients.

BuChE, which occurs in glia cells that are located near neurons, is a second enzyme that breaks down ACh. Of all 3 cholinesterase inhibitors, only rivastigmine inhibits this enzyme (2C), which might be particularly advantageous in the later stages of Alzheimer's disease.

Presynaptic and postsynaptic nicotinic cholinergic receptors mediate many of the actions of ACh on attention and memory. Of all 3 ChE inhibitors, only galantamine allosterically modulates nicotinic receptors (2D). Galantamine may also serve as a possible aid to improving cognition and behaviors related to depression and anxiety.