Experimental AD Drugs Target Nicotinic Receptors

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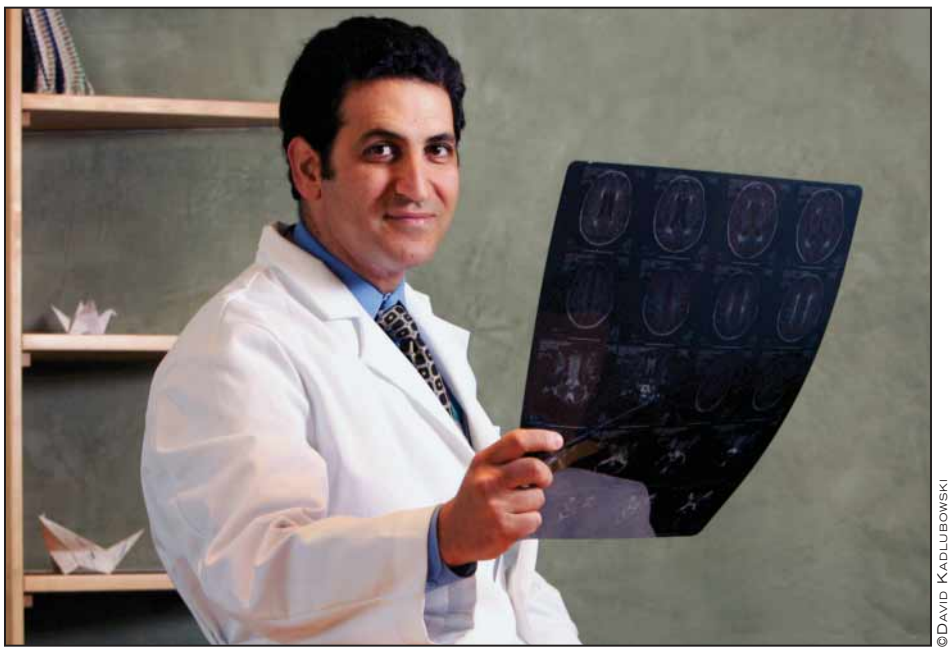
A new class of drugs under development for Alzheimer's disease has taken a cue from one of the world's oldest drugs—nicotine.

The highly selective nicotinic receptor agonists (NRAs) have the potential to mimic, and surpass, the cognition-enhancing effects of nicotine without its cardiovascular or addictive side effects. Tantalizing evidence suggests that the engineered molecules could provide a therapeutic one-two punch for Alzheimer's patients: immediate cognitive improvement and protection against the amyloid β plaques and neurofibrillatory tangling that are the disease's hallmarks.

Brains of patients with Alzheimer's disease (AD) show another distinct characteristic: a significant loss of cholinergic neurons and acetylcholine receptors, in addition to the hallmark plaques and tangles, said Dr. Marwan Sabbagh, a neurologist and director of the Sun Health Research Institute's Cleo Roberts Center for Clinical Research in Sun City, Ariz. "Initially, it was thought that muscarinic receptors were selectively affected in Alzheimer's, but now we think that's not so," he explained. "It seems that the nicotinic receptors are the ones that go."

Nicotinic acetylcholine receptors (nAChRs) are activated by acetylcholine, but they also react to nicotine and structurally similar molecules. Two types of nAChRs, the α7 and the α4-β2, are richly distributed in areas of the brain targeted by Alzheimer's. Other types of nAChRs occur in skeletal muscle and gut tissue.

Postmortem studies have shown that up to 50% of nAChRs are lost in Alzheimer's brains. This is apparently related to the buildup of amyloid β plaques, which seem to preferentially attach to the α7 nAChRs, the type most highly expressed in the hippocampus and frontal cortex, Dr. Sabbagh said in an interview. "High affinity α4-β2 receptors are preferentially lost in AD but the α7 receptor is expressed in plaques. This suggests that the biological interaction between the nicotinic receptors and AD pathology is complex," he said.



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Dr. Marwan Sabbagh says nicotinic acetylcholine receptor agonists must boost the activity of high-affinity receptors in the brain but not nicotinic receptors elsewhere.

A selective nAChR agonist could improve cholinergic function in a couple of ways, Dr. Sabbagh said. The surviving receptors would become more sensitive to any available acetylcholine. And since nAChRs help modulate the flow of other neurotransmitters, boosting their function could improve levels of dopamine, norepinephrine, and γ-amino butyric acid as well.

But since nAChRs are distributed throughout many tissues, a compound that attaches nonselectively could be loaded with adverse effects. "The challenge is to develop a selective agonist that enhances the activity of the high-affinity receptors in the brain, but not the nicotinic receptors that occur in the muscles, the gastrointestinal tract, or anywhere else."

Drug companies are hot on the trail of such compounds. At least three agonists that target receptors involved in cognitive impairment are in preclinical or clinical trials right now. These three are described in the following paragraphs.

Targacept Inc. of Winston-Salem, N.C., a spinoff company of tobacco giant R.J. Reynolds, is farthest along the developmental pipeline with its candidate, TC-1734. In 2004, the company completed two phase II safety trials of the drug for age-associated memory impairment and mild cognitive impairment, with a total 107 patients. According to the company Web site, the drug had positive effects on cognition.

Last month, Targacept completed a second trial in 193 cognitively impaired older adults, but company representatives declined to comment for this article, saying they were constrained by the quiet period surrounding their initial public stock offering in January.

Memory Pharmaceuticals Corp. of Montvale, N.J., recently announced positive findings from its phase I trial of MEM 3454 in 48 healthy young subjects. Cognitive performance, a secondary end point of this safety trial, significantly improved in those taking 15 mg daily, said David A. Lowe, Ph.D., the company's chief scientific officer.

The trial lasted 14 days and tested three doses (15 mg, 50 mg, and 150 mg). Only the 15-mg dose showed a statistically significant effect on cognition. "One particularly interesting observation was that the effect on day 13 was stronger than it was on day 2," Dr. Lowe said in an interview. "This shows that the effect is sustained." The company will proceed with a phase IIa trial later this year.

Abbott Laboratories has a number of NRAs in the works, said James Sullivan, Ph.D., the company's vice president of neuroscience research. ABT-089 had proceeded to phase II trials in adults with attention-deficit hyperactivity disorder, but is now back in the preclinical stage for additional toxicologic studies. The drug also has potential as an Alzheimer's therapy, Dr. Sullivan said.

Although there are no published data on neuroprotective effects of any of the NRAs in development, studies suggest that nicotine blocks the aggregation of amyloid β on neurons. If NRAs work the same way, they might reduce or prevent neuronal plaque buildup.

But a study released last year concluded that the compounds could actually worsen the other major component of Alzheimer's pathology: neurofibrillatory tangling.

Frank LaFerla, Ph.D., and colleagues administered daily nicotine to mice genetically engineered to develop amyloid β plaques and neurofibrillatory tangling. After 5 months, their brains showed significant accumulation of tau in pyramidal neurons—a preliminary event in tangle formation—and significant increases in phosphorylated tau, a protein found in the tangles (PNAS 2005;102:3046-51).

"That doesn't mean that there isn't a place for NRAs," said Dr. LaFerla, codirector of the Institute for Brain Aging and Dementia at the University of California, Irvine. "Nicotine is a pretty dirty drug and probably has other effects than just binding to the receptor. If you could come up with a more selective compound, you might still see a beneficial effect."

An Alzheimer's drug that would provide quick cognitive benefits and progressive disease modification would have enormous impact, according to Dr. Peter Whitehouse. But disappointment over past efforts to enhance the cholinergic system, including today's cholinesterase inhibitors, has provoked concern about this new pharmacotherapy.

"Maybe if the cholinesterase inhibitors had worked better, we'd be seeing a different climate for NRAs," said Dr. Whitehouse, professor of neurology at Case Western Reserve University, Cleveland. "It will be a challenge to find drugs with an effect size much larger than current cholinesterase inhibitors." ■

Eleven Deaths Reported in Donepezil Vascular Dementia Trial

Eleven of 648 patients died while taking donepezil (Aricept) in a trial of the drug for the treatment of vascular dementia, according to preliminary study results announced by Eisai Co. Ltd., the drug's maker. None of the 326 patients taking placebo during the 24-week trial died.

The multicenter, randomized, double-blind study was conducted in nine countries and enrolled only people with vascular dementia (VaD), who had no prior diagnosis of Alzheimer's disease. Donepezil is currently approved only for the treatment of mild to moderate Alzheimer's disease in the United States.

Those patients taking donepezil showed improvement on measures of cognition, compared with those on placebo. However, there was no benefit observed on global function, the trial's other primary measure.

An analysis of adverse events data revealed that the mortality rate of 1.7% for the donepezil treatment group in this trial was consistent with that observed in a combined analysis of two previous VaD studies (1.7%) and was lower than that reported in the general population of patients with vascular dementia. However, the mortality rate observed in the placebo group of this study (0%) was lower than that seen in the placebo groups in the combined analysis for the two prior VaD studies (2%), and was lower than the rate for the general VaD population.

In an analysis of all three vascular dementia trials, observed mortality rates were not statistically significant between the donepezil-treated group and the placebo group (1.7% vs. 1.1%).

Additional analyses of vascular events such as stroke and myocardial infarction for the three VaD trials, alone and combined, showed a statistically significant higher risk of a vascular event in the donepezil group, compared with placebo.

In the most recent study, overall adverse events were not significantly different between the treatment and placebo groups. Adverse events in the treatment group occurred at a rate greater than 5%, and twice the rate of placebo, for abdominal pain (5.1% vs. 2.5%), anorexia (5.7% vs. 2.8%), and nausea (9.9% vs. 4.3%).

Eisai has notified regulatory authorities about the mortality findings, and has reported that the results of the most recent vascular dementia study have not changed the overall safety profile of the drug, and that the drug's benefit-risk profile continues to be favorable for its approved indications.

—Kerri Wachter