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Discovery May Alter Approach to CNS Drug Delivery

BY JEFF EVANS

FROM SCIENCE TRANSLATIONAL MEDICINE

In the process of developing a more efficient way to get an experimental antibody therapy across the blood-brain barrier to treat Alzheimer's disease, researchers may have raised the prospects for delivering therapeutic antibodies to the brain for other diseases.

Investigators at Genentech tested an antibody targeting beta-secretase, or beta amyloid cleavage enzyme 1 (BACE1), which creates the amyloid-beta (Abeta) peptide fragments that are believed to play a pathological role in Alzheimer's disease. They found that the anti-BACE1 antibody significantly reduced Abeta in the blood of mouse models of Alzheimer's disease and in monkeys. But brain Abeta levels were not substantially reduced.

In their experiments with anti-BACE1, Jasvinder K. Atwal, Ph.D., and colleagues found that unlike existing small-molecule inhibitors of BACE1, the antibody binds to an epitope outside of BACE1's active site and is specific only to BACE1 and not other related enzymes, such as BACE2 or cathepsin D (Sci. Transl. Med. 2011;3:84ra43).

In primary neuron cultures, anti-BACE1 significantly reduced the synthesis of Abeta peptides, whereas in mouse and monkey models of Alzheimer's disease the antibody lowered serum concentrations of Abeta by about 50%. However, concentrations of Abeta in the brains of mice declined only modestly after administration of anti-BACE1. Reductions in amyloid-beta also were observed in the cerebrospinal fluid of cynomolgus monkeys that were given anti-BACE1, serving as a proxy for brain exposure, but also were transient and lasted only 7 days. At the anti-BACE1 doses given to these animals (3 mg/kg, 30 mg/kg, and 100 mg/kg), the median inhibitory concentrations were still less than what were observed in primary neuron cultures.

To address the difficulties of anti-BACE in reaching therapeutic levels in the brain, Dr. Atwal and other researchers at Genentech, led by Y. Joy Yu, co-opted a cellular process called receptor-mediated transcytosis to cross the blood-brain barrier (BBB) and increase the concentration of an anti-BACE1 antibody in the brain (Sci. Transl. Med. 2011;3:84ra44).

This transport process normally moves macromolecules from one side of a cell to another, and is thought to assist in bringing circulating blood proteins (such as insulin and transferrin) to the brain via the capillary endothelial cells of the BBB.

In mice, Ms. Yu and her coauthors created a new antibody against BACE1 that also has low affinity for the transferrin receptor (TfR), allowing the receptor to carry it across the BBB but also dissociating the antibody readily from the receptor once it has done so. When administered to mice intravenously, this anti-TfR/BACE1 antibody was broadly distributed in the brain and reached higher, therapeutic concentrations than did anti-BACE1. At doses of 50 mg/kg, anti-TfR/BACE1 reduced Abeta peptides in the brain by 50% at 48 hours, compared with 18% for anti-BACE1.

The investigators noted that "although the anti-TfR antibody used in this study does not block binding of transferrin to TfR, the acute and chronic safety considerations of using antibodies raised against TfR to increase uptake in brain have not been explored."

They concluded that their "findings demonstrate substantial promise for brain-penetrating bispecific therapeutic antibodies that exploit receptor-mediated transcytosis, and provide evidence that this approach may be useful in targeting a wide range of CNS diseases with antibody therapy."

All of the investigators in both studies are employees of Genentech, which funded the research. Genentech has filed patent applications related to this work. ■

ADVISER'S VIEWPOINT

Second Life for Alzheimer's Drug Target?

Alzheimer's disease is the most common type of dementia found in the elderly, and its frequency and financial burden on families and societies are expected to skyrocket in the coming decades as the population age increases worldwide. Currently, there are 5.4 million Americans with Alzheimer's and 27 million worldwide. The financial impact of the disease is $160 billion, and the pharmaceutical market is estimated to be $4 billion.

The pathology features brain extracellular deposits of amyloid-beta peptides that form senile plaques and intraneuronal tangles that are made up of tau protein (Physiol. Rev. 2001;81:741-66). Both plaques and tangles are formed over several years, and only when the neuronal loss is pronounced do symptoms appear. To date, no disease-modifying treatments are approved for Alzheimer's, and new therapeutic approaches need to be explored by first using animal models of the disease.

Amyloidogenesis, the process by which amyloid-beta (Abeta) is produced, stems from the consecutive endoproteolysis of the amyloid precursor protein by beta- and gamma-secretases to generate peptides of different lengths, including Abeta40 and Abeta42, which are the main components of senile plaques (Ann. Med. 2008;40:562-83). Beta-secretase is the rate-limiting enzyme in the process. Genetic manipulations in mice have shown that the major beta-secretase in the brain, and likely in Alzheimer's, is BACE1 (Nat. Neurosci. 2001;4:231-32). Therefore, intensive effort has been invested into the development of specific BACE1 inhibitors that can cross the BBB, but none has been successful until now.

The reports by Dr. Atwal and Ms. Yu and their colleagues offer encouraging news about the development of selective anti-BACE1 antibodies and anti-TfR antibodies. These reports are encouraging because targeting gamma-secretase with inhibitors has been fraught with systemic complications, including hematologic, GI, and more recently, neoplastic. Complicating matters further for gamma-secretase inhibitors (GSIs) is the report that the GSI semagecestat was halted in phase III clinical trials (CLINICAL NEUROLOGY NEWS, October 2010, p. 15). Thus, enthusiasm for GSIs has waned. BACE inhibitors have been of interest for some time but until recently, no compelling compounds have emerged.

BACE1 antibodies would be desirable because they are more specific to the Alzheimer's disease process and pathophysiology. Still, antibodies are confounded by BBB permeability issues, and so enthusiasm for the reports by Dr. Atwal and Ms. Yu will need to be tempered until we are further along in the drug development process. Enthusiasm for amyloid approaches is waning overall. However, critical consideration should be given to not only whether anti-amyloid approaches are appropriate but also the timing of administration of these approaches. Until now, all GSIs and immunotherapies have been administered to symptomatic individuals who are carrying established and heavy amyloid burdens. One has to wonder whether these agents would be more effective if administered earlier in the disease process.

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Little Evidence Supports Psych Meds for Alzheimer's Patients

BY NEIL OSTERWEIL

FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR GERIATRIC PSYCHIATRY

SAN ANTONIO – Hard evidence supporting the use of either atypical antipsychotics or antidepressants in Alzheimer's disease patients remains scant, according to Dr. Daniel Weintraub.

Dr. Weintraub of the departments of psychiatry and neurology at the University of Pennsylvania, Philadelphia, said that although older adults with Alzheimer's disease (AD) frequently are prescribed atypical antipsychotics to control psychosis, aggression, or agitation, the drugs also are associated with significant adverse events and a long-term increase in mortality risk in this population.

At the meeting, he noted that investigators in a 42-site, placebo-controlled trial of 421 patients with Alzheimer's and psychosis found that the adverse effects of the agents offset possible advantages (N. Engl. J. Med. 2006;355:1525-38).

Adverse events included an increase in parkinsonism and/or extrapyramidal symptoms with olanzapine and risperidone, which occurred in 12% of patients on each drug, compared with 2% for quetiapine. All three of these agents were associated with increased sedation, compared with placebo, and olanzapine and risperidone were both associated with more confusion and changes in mental status than was placebo, said Dr. Weintraub, who is also a psychiatrist at the Philadelphia VA Medical Center.

Long-term follow-up from the DART-AD (Dementia Antipsychotic Withdrawal trial) also showed that antipsychotics were associated with an increased long-term risk of mortality in patients with AD (Lancet Neurol. 2009;8:151-7).

In the Depression in Alzheimer's Disease–2 trial, no evidence of efficacy was found for the use of sertraline for the treatment of depressive symptoms in patients with AD, and an increase in adverse events was found, including a doubling of dry mouth and diarrhea vs. placebo, as well as a near trebling of dizziness. Sertraline also was associated with a significant increase in pulmonary adverse events at 24 weeks, compared with placebo.

Dr. Weintraub has received honoraria from Novartis Pharmaceuticals, Boehringer Ingelheim, Merck Serono, and Labopharm Pharmaceuticals. ■