Image of the Month

N-methyl-[11C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, better known as Pittsburgh Compound B (or simply PIB), has been long anticipated in Alzheimer's disease circles. The PET radiotracer allows researchers and clinicians to see amyloid plaque deposition in live human subjects, opening up a number of investigational and clinical possibilities.

Although the exact binding mechanism is unknown, the compound is derived from thioflavin T, a dye used in autopsy tissue studies to highlight amyloid fibrils in the brain, said Dr. William E. Klunk, of the department of psychiatry at the University of Pittsburgh, who—along with Chester Mathis, Ph.D., professor of radiology and director of PET at the university—developed the compound.

To assess the correlation between PIB binding and amyloid deposition in the brain, the researchers recently homogenized the tissue from several Alzheimer's disease (AD) brain samples and then split the homogenates for analysis with Aβ ELISA (amyloid-β peptide enzyme-linked immunosorbent assay). "They line up very nicely," said Dr. Klunk. In human brains, the PIB binds in a 1:2 ratio with amyloid. They also performed in vitro binding studies (J. Neuroscience 2005;25:10598-606).

The imaging technique allows researchers and clinicians to follow disease progression over time, and may also allow researchers to identify patients earlier in the disease process.

It's unclear how early in the course of amyloid deposition PIB imaging can reveal this process. "We can see amyloid in some clinically normal elderly controls. We can see amyloid in some Down syndrome subjects who haven't developed any signs of clinical deterioration, but most interesting is the fact that we can see amyloid deposition in people who carry presenilin 1 or Aβ (A4) precursor protein gene mutations," said Dr. Klunk. In fact, the researchers have looked at individuals with these risk factors who were as young as age 35 years, and have found amyloid deposition. The typical age of clinical onset in these individuals is the late 40s.

The exact relationship between AD and amyloid deposition in the brain remains elusive. "Not having clinical symptoms, in my mind, does not equate with not having a disease, if you have the pathology. The question is, do you care about having the pathology if you don't have the clinical symptoms?" Dr. Klunk likens the presence of amyloid in patients who will go on to develop AD to the presence of plaque in the carotid artery: The earlier you know about it, the better. The success in finding an intervention that can prevent disease progression "will determine whether this imaging technique becomes extremely important in the management of patients with AD, or remains [just] an interesting research technology," said Dr. Klunk.

PIB stands to play a role in the development of a drug that can halt or even prevent amyloid deposition. "We're currently using this technology in collaboration with pharmaceutical companies to look at their antiamyloid agents … to see if these drugs are having an effect on the target," he said.

Using this technology both "to show that you can remove amyloid from a living person and to monitor that" and "to find the right people to use it on early enough" will be key, he said.

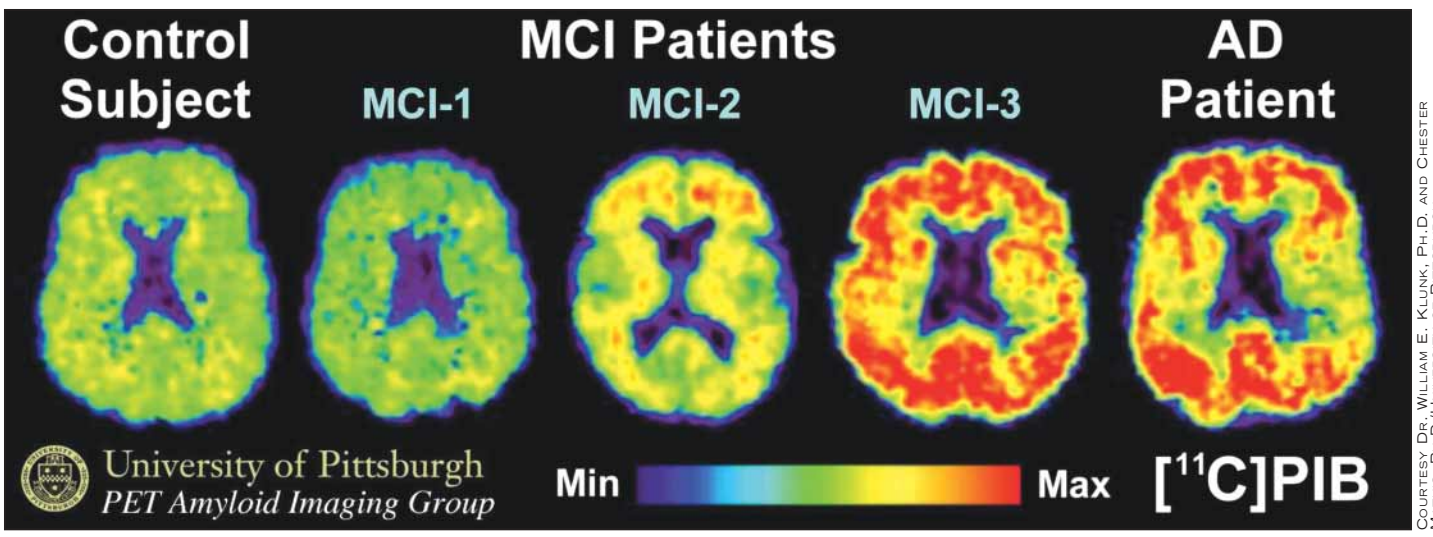
In the images of patients with mild cognitive impairment (MCI), the degree of clinical severity did not correlate with the presence or absence of amyloid deposition. (See photo.) "About 30% of [MCI patients] have no signs of amyloid deposition. That happens to be an interesting number because, in our center, about 30% of our MCI patients never develop AD. The question is, are these amyloid-negative MCI cases the same 30% who won't develop AD?"

The MCI PIB-negative cases—note particularly the MCI 1 image in the photo—are virtually indistinguishable from control subjects on PET. Similarly, the images of MCI 3 patients—who make up the majority of MCI cases—are virtually indistinguishable from the images of patients with AD. Only 15%-20% of MCI cases look like the MCI 2 image. "That transitional phase probably occurs before the MCI phase on most cases in the MCIs that are going to get amyloid deposition in AD," said Dr. Klunk.

PIB imaging may also help researchers investigate potential risk factors. The researchers are currently using the technique to assess the relationship between depression and AD. Research indicates that many elderly patients with depression will develop AD. The researchers want to determine if the elderly depressed patients with amyloid are the ones who go on to develop AD, and whether the patients without amyloid are the ones who will recover and not develop AD. Although most of the results of PIB's promise remain down the road, the technique has clinical applications today. PIB imaging may be useful in cases of clinically confusing dementia. "We'd love to find out if there is amyloid in the brain to help root out these diagnoses," said Dr. Klunk.

Along with their colleague Dr. Steven DeKosky, chair of the neurology department at the University of Pittsburgh, the researchers are currently using the technique in patients with dementia of unknown origin.

—Kerri Wachter



Courtesy Dr. William E. Klunk, Ph.D. and Chester Mathis, Ph.D./University of Pittsburgh

PET with PIB reveals differences in amyloid deposition between cognitively normal subjects (far left) and subjects with AD (far right). PET with PIB also reveals the range of amyloid accumulation in subjects with clinically mild cognitive impairment (center).

Drugs Being Tested

Nicotinic Receptors *from page 1*

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.

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. 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 of 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). "One particularly interesting observation was that the effect on day 13 was stronger than it was on day 2," Dr. Lowe said.

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.

NRAs may offer more than symptomatic improvement for Alzheimer's. 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.

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. ■

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