Cooling down AD

By Lev Osherovich, Senior Writer

A team from **The Johns Hopkins University** has clinical proof of concept for an unconventional approach to slowing the progression of Alzheimer's disease—reducing activity in the hippocampus with antiepileptic drugs.¹ Based on the findings, **AgeneBio Inc.** has licensed patent applications from the university on lowering brain activity with antiepileptic drugs to prevent AD.

The standard view of AD etiology holds that the disease results from neuronal loss in the hippocampus caused by aggregated β -amyloid ($A\beta$). The hippocampus normally facilitates memory formation and recall, but the brain region degenerates early during AD, causing lapses in short-term memory.

Multiple groups including a JHU team led by Michela Gallagher had previously found evidence of abnormally high activity in the hippocampus in patients with AD and in preclinical models of AD,² but it was unclear whether the excess activity was a cause or consequence of the disease.

Now, Gallagher's group has shown that reducing hippocampal activity with the antiepileptic drug levetiracetam actually improved memory task performance in patients with mild cognitive impairment (MCI), a condition that precedes full-blown AD.

"The story of excessive hippocampal activity in mild cognitive impairment patients has been known for some years," said Gallagher, who is a professor of psychology and neuroscience. "People had previously seen this as evidence that because memory is failing, the hippocampus is compensating by doing extra work."

The new study provides the strongest evidence yet in favor of the hypothesis that excessive hippocampal activity drives AD progression, rather than the other way around.

It has been difficult to test the relationship between epilepsy and AD in the clinic because many patients with AD experience epilepsy-like seizures, and many patients with epilepsy experience AD-like memory problems.

Other researchers have seen evidence that $A\beta$ aggregates can induce an epilepsy-like state of hippocampal hyperexcitability,³ but the relationship between $A\beta$ and epilepsy-like hippocampal activity remains murky.

Gallagher thinks that focusing on $A\beta$ is a red herring. Instead, she advocates normalizing the hyperactivity of hippocampal neurons by

targeting upstream neurons that are known to go awry in epilepsy.

Speak, memory

Gallagher's team used MRI to visualize hippocampal activity in 17 patients with MCI and 17 age-matched controls. In image-matching tasks that required short-term recall, patients had impaired performance and higher levels of activity in the dentate gyrus and CA3 hippocampal regions compared with controls.

Next, the group treated the patients with a low dose of Keppra levetiracetam, a synaptic vesicle protein (SV2A) ligand marketed by **UCB Group** for partial-onset seizures, myoclonic seizures and primary generalized tonic-clonic seizures.

A two-week course of the drug decreased hippocampal activity during the memory task ($p=0.022$) compared with placebo and produced a modest but significant improvement in patients' performance at image matching ($p=0.026$). No difference was seen between the groups two weeks after dosing was stopped.

The findings were reported in *Neuron*. JHU has filed patents on using antiepileptic drugs to treat AD and has licensed the IP to AgeneBio, which Gallagher founded in 2008.

Lennart Mucke, professor of neurology and neuroscience at the **University of California, San Francisco** and director of the **Gladstone Institute of Neurological Disease**, said Gallagher's findings are in line with unpublished preclinical studies in his own laboratory.

He said clinical evidence of epilepsy-like hyperactivity in the brains of patients with AD has led him and Gallagher to investigate the effect of epilepsy drugs in rodent models of the disease.

"Levetiracetam turns out to be efficacious at suppressing abnormal brain wave activity in mouse models of AD, where it is also beneficial in terms of synaptic function and cognitive impairment," said Mucke.

Two big unknowns are the mechanism by which excessive hippocampal activity contributes to AD and how levetiracetam interferes with the disease process.

According to Gallagher, hyperexcitability of hippocampal neurons arises from age-related dysfunction in upstream inhibitory interneurons that develops independently of $A\beta$ -related AD pathology. In this view, hippocampal activity increases as a natural consequence of aging, but in some people the excess activity combines with AD mechanisms to render the hippocampus especially sensitive to the effects of aberrant $A\beta$ and microtubule-associated protein- τ (MAPT; TAU; FTDP-17), which is another AD-linked protein.

"My view is that the hippocampal hyperexcitability is a permissive factor that occurs in the background of other disease processes" such as $A\beta$ and TAU aggregation, said Gallagher.

Further preclinical studies of levetiracetam's effects could uncover how the drug affects well-validated biomarkers of AD such as $A\beta$ and TAU levels, said John Cirrito, assistant professor of neurology at the **Washington University in St. Louis**.

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**—Michela Gallagher,
The Johns Hopkins University**

“One possibility is that the drug is directly suppressing A β levels, but there is no evidence for that yet,” said Cirrito.

“This drug has several modes of action,” said Mucke. “One is that it binds to SV2A and could change the release of neurotransmitters.

“One possibility is that the drug is directly suppressing A β levels, but there is no evidence for that yet.”

**—John Cirrito,
Washington University in St. Louis**

It's also reported to affect glutamate transporters, potentially counteracting excitatory activity caused by glutamate.”

Commercial plans

Gallagher thinks the antiepileptic strategy is ready for broader clinical

testing. Her challenge is to improve the drug's efficacy. Her team's preclinical work showed that increasing the dose of the drug actually worsened cognitive performance.

She does think the modest effect of the drug on functional performance could be improved by longer dosing. Gallagher suspects that chronic treatment with low doses of levetiracetam might lead to sustained functional improvement and might even slow the progression

of MCI into AD.

AgeneBio plans to advance an undisclosed compound that is related to levetiracetam into a Phase II trial in patients with MCI. The company did not disclose when that trial would begin. AgeneBio also has a compound that targets GABA_A receptor, another epilepsy target, in preclinical development for AD.

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COMPANIES AND INSTITUTIONS MENTIONED

AgeneBio Inc., Carmel, Ind.

Gladstone Institute of Neurological Disease, San Francisco, Calif.

The Johns Hopkins University, Baltimore, Md.

UCB Group (Euronext:UCB), Brussels, Belgium

University of California, San Francisco, Calif.

Washington University in St. Louis, St. Louis, Mo.