Hyperactive Hippocampus: Response or Root Cause?

Quieting Memory-Related Brain Structure Can Improve Memory

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Scientists at Johns Hopkins University reported that they were able to improve memory in patients with amnestic mild cognitive impairment – a neurological condition somewhere between normal age-related memory loss and outright dementia that often progresses to Alzheimer's disease – by treating them with low doses of the anti-epileptic drug Keppra (levetiracetam, from Brussels, Belgium-based UCB SA).

The drug appears to work by reducing activity in the hippocampus, a brain structure that is important for memory formation. Hippocampal activity is increased during amnestic mild cognitive impairment, as well as in individuals from families with familial Alzheimer's disease, even before those individuals have developed outright Alzheimer's disease themselves.

When it was first discovered, such increased activity was "initially thought to be more of a compensatory change," Sharon Rosenzweig-Lipson told BioWorld Today. Rosenzweig-Lipson is vice president of research at AgeneBio, a startup that is in clinical trials with Keppra.

In response to failing memory, the hippocampus was thought to go into a kind of overdrive. But the new study adds to the evidence that rather than being a response to the problem of worsening memory, excess hippocampal activity may be responsible for it, at least in part.

Most approaches to Alzheimer's disease focus on amyloid-beta accumulation and, to a lesser extent tau protein. Those two proteins are responsible for the plaques and tangles that are the most striking anatomical features of brains with Alzheimer's disease, and multiple trials have attempted to make a dent in Alzheimer's by targeting them directly, or the enzymes that produce them.

The idea that altered neural activity is important in Alzheimer's does not necessarily contradict the importance of those proteins. Recent research by other groups, in fact, has shown that beta-amyloid proteins may be regulated in part by neuronal activity.

But, Rosenzweig-Lipson said, they approach the problem "from a different perspective, [namely], what's happening with the circuitry, and how do we address the circuitry?"

Other researchers are also looking for ways to focus on neural activity instead of amyloid beta. (See BioWorld Today, May 2, 2012.)

And certainly, drug discovery for Alzheimer's disease can use some fresh ideas. The last 14 Phase III trials of Alzheimer's drug hopefuls have failed, most recently the CONCERT trial of Medivation Inc.'s Dimebon (laterpirdine). (See BioWorld Today, Jan. 18, 2012.)

In their work, which was published in the May 10, 2012, issue of Neuron, senior author Michela Gallagher, who is a professor of psychology and neuroscience at Johns Hopkins University and a founder of AgeneBio, and her team first used magnetic resonance imaging to compare the levels of brain activity in either normal subjects or those with amnestic mild cognitive impairment.

They found that the latter group had higher levels of activity in their left hippocampus. Rosenzweig-Lipson said that it was not necessarily surprising that only one side of the hippocampus showed greater activity for the particular task used in their experiments, since hippocampal activation depends on the specifics of the task.

The researchers then treated the patients with amnestic mild cognitive impairment with either low doses of Keppra, taken twice daily for two weeks, or placebo. Healthy controls received placebo throughout the study.

The team repeatedly both measured the brain activity of their subjects, and tested them on a memory task where they were shown pictures and had to identify each picture as new, old, or new but similar to one they had seen before.

They found that this treatment regimen reduced the level of hippocampal activity in the amnestic subjects so that it was no longer different from those of controls. Patients also improved in their ability to tell whether a picture was similar to one they had seen before, or new.

Notably, in the experiments reported in Neuron, treatment did not improve the patients' performance on more general memory tests. (COMMENT)

AgeneBio has intellectual property related to Keppra's use in memory loss, and also has earlier programs based on its own compounds. A dose-finding Phase II trial investigating Keppra's effects on memory is currently underway at Johns Hopkins, and Rosenzweig-Lipson said the company is "looking to initiate Phase IIb trials" once it is complete, likely later this year.