Researchers find drugs being tested for Alzheimer's disease work in unexpected and beneficial ways

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Researchers at Mayo Clinic, with their national and international collaborators, have discovered how a class of agents now in testing to treat Alzheimer's disease work, and say they may open up an avenue of drug discovery for this disease and others.

In the June 12 issue of *Nature*, they report that agents known as gamma-secretase modulators (GSM) work to reduce production of long pieces of the amyloid beta protein (Abeta) that readily stick together and form clumps, and increase production of shorter Abeta that can inhibit the longer forms from sticking together.

This is critical because only when Abeta aggregates and accumulates is it harmful and can trigger Alzheimer's disease, the researchers say.

"So, as these compounds lower the amount of the bad, longer sticky Abeta peptides in the brain, they increase the quantity of shorter Abeta peptides that may protect against development of Alzheimer's disease," says senior author Todd Golde, M.D., Ph.D., Chair of the Department of Neuroscience at Mayo Clinic in Jacksonville.

"In a very general sense the action of these GSM on Abeta might be analogous to some cholesterol lowering drugs that can lower LDL, the bad cholesterol that sticks to your arteries, and can raise HDL, the good cholesterol that sweeps out LDL," he says.

Not only that, GSM agents actually stick to the Abeta already in the brain, keeping it from aggregating. A hallmark of Alzheimer's is formation of "plaques" and other assemblies of Abeta protein in the brain, which are believed to damage neurons in complex ways that are not yet fully understood, researchers say. "Surprisingly, this means that these compounds may do three things that may be beneficial with respect to Alzheimer's disease: they inhibit production of long Abeta, block aggregation of Abeta, and increase production of shorter Abeta peptides that may in turn inhibit Abeta aggregation," says the study's lead investigator, Thomas Kukar, Ph.D.

As exciting as these discoveries are, the investigators – which number 29 in all and are from four nations - also found that GSMs work in a way that has not been seen before in other drugs. "Most drugs target enzymes, which act on proteins, or cell surface receptors, which proteins bind to," he says. "These agents work on the structure, or substrate, of the protein itself, which had not been believed to be druggable."

"This broadens the notion of what drugs can do, and therefore, has wide reaching implication for future drug discovery for many different disorders," Dr. Golde says.

The findings also suggest that GSMs now being tested or in development to treat Alzheimer's may prove to be valuable, the researchers say. One such drug, tarenflurbil (FlurizanTM), is in Phase III clinical trials, and results from the first, a 1,600-patient US study, are expected this summer. Results of a phase II study, published online in April in Lancet Neurology, suggest it provides benefit in patients with mild Alzheimer's, Dr. Golde says.

Understanding the agent Mayo discovered

Mayo Clinic helped discover that tarenflurbil was a GSM. Previously,

Dr. Golde, along with Eddie Koo, M.D., of the University of California at San Diego, found that the agent tarenflurbil, then called r-flurbiprofen, inhibited production of Abeta 42, and increased the quantity of the shorter Abeta38 but they did not know why. Myriad Genetics, a biotechnology company, had been testing the drug to treat prostate cancer, an indication that is not currently being pursued. But after cell and animal studies in the laboratories of Dr. Golde and Dr. Koo suggested that tarenflurbil could influence Abeta production and reduce cognitive deficits in a mouse model of AD, the company began testing it to treat Alzheimer's in humans.

At the same time, Mayo researchers, led by lead investigator Thomas Kukar, Ph.D., worked to understand how tarenflurbil and other so-called GSMs work. The Abeta protein is normally generated from a larger protein (the amyloid precursor protein) by the sequential cutting action of two different enzymes that act as molecular scissors. Such enzymes that cut other proteins are referred to as proteases. First the protease, beta-secretase, cuts the protein above the cell membrane.

A second protease, gamma-secretase, then clips the portion that sticks inside the cell. Where gamma-secretase cuts the amyloid precursor protein determines how long the Abeta peptide will be. The most commonly produced fragment is Abeta 40, but some are longer (Abeta 42) and some, such as Abeta 38, are shorter. None clump together as quickly as Abeta 42 does, however, and emerging evidence indicates that these shorter pieces may actually keep the longer Abeta 42 from clumping together.

The discovery of gamma-secretase initially led to development of agents designed to block its action. One strategy was to directly target and block gamma-secretase, but because the protease acts on many different proteins, this approach proved to be too toxic, Dr. Golde says. Companies then focused on developing "selective" scissor targeting

gamma-secretase inhibitors that predominantly inhibit Abeta production without affecting other targets of the protease. At least one such compound, tarenflurbil, is in clinical trials with several more expected to be entering human trials over the next year or two.

Researchers at Mayo thought that tarenflurbil must also be directly targeting gamma-secretase, but it took almost three years of experimentation using multiple methods to discover that the agent actually acts on the substrate of the scissors –the amyloid precursor protein itself. It is thought that the compounds somehow push the protein around in the membrane so that when the gamma-secretase scissors finally cut it, toxic abeta 42 fragments are not produced.

Relevance for future drug discovery

"We now think most GSMs, including tarenflurbil, work this way," Dr. Kukar says. "This is one of the few examples of a small molecule drug that targets a protein substrate rather than the enzyme that works on it, and from a therapeutic point of view, that can offer many beneficial effects."

"If results from tarenflurbil and other GSM agents are less beneficial than hoped, these findings may help drug designers create newer, more potent drugs," Dr. Golde says. "Anytime we gain an increased understanding of the precise molecular action of a drug, that enhances our ability to make better drugs."

Source: Mayo Clinic

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