ALZHEIMER'S DISEASE

Bad for the Heart, Bad For the Mind?

High cholesterol levels may foster the brain degeneration of Alzheimer's, raising the possibility that cholesterol-lowering drugs will protect against the disease

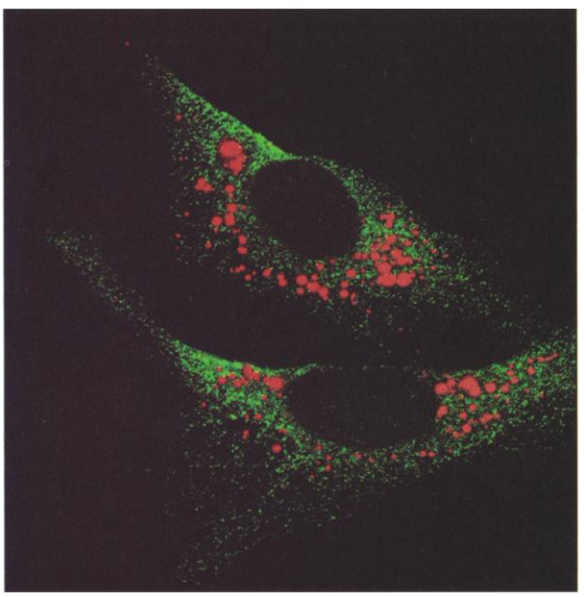
Cholesterol has a bad reputation, and justifiably so, because elevated levels increase the risk of cardiovascular diseases such as heart attack and stroke. But it may deserve even more condemnation. Accumulating evidence suggests that high cholesterol levels contribute to Alzheimer's disease as well.

Researchers have built a case over the past few years that a small protein called β amyloid (Aβ) causes the brain degeneration of patients with Alzheimer's. But they have also suspected that Aβ has accomplices. High blood cholesterol levels may be one of these malefactors, possibly because they aid and abet Aβ production, several teams now suggest. "It looks like cholesterol is involved [in Alzheimer's] in some fashion," says Neil Buckholtz, who oversees Alzheimer's research at the National Institute on Aging (NIA) in Bethesda, Maryland.

If so, cholesterol may provide "an accessible and straightforward target for decreasing Aβ and reducing Alzheimer's risk," says Joseph Buxbaum of Mount Sinai School of Medicine in New York City. Indeed, NIA has just announced that it will expand its ongoing Alzheimer's Disease Cooperative Study (ADCS) to include a trial aimed at determining whether the cholesterol-lowering drugs called statins slow the progression of mild to moderate Alzheimer's. A similar trial is already under way at the Sun Health Research Institute in Sun City, Arizona, and researchers in Europe are also looking at statins' effects on Alzheimer's.

One of the first clues that cholesterol might be involved in the disease came about 10 years ago from Larry Sparks and his colleagues at the University of Kentucky Chandler Medical Center in Lexington. Sparks, then a forensic pathologist, was often called upon to perform autopsies on people who had died unexpectedly. He noticed that about 70% of individuals who had succumbed to heart disease also had amyloid-containing plaques—one of the defining features of Alzheimer's pathology—in their brains. People of about the same age who had died of other causes were much less likely to have plaque-ridden brains, leading Sparks to suspect a link between high cholesterol levels and Alzheimer's.

That was far from proof, however; impaired blood flow to the brain or other factors might explain why heart disease victims developed so many plaques. But 2 years later, the cholesterol connection got a boost when a genetic linkage study by Allen Roses, Warren Strittmatter, and their colleagues at Duke University School of Medicine in Durham, North Carolina, identified a particular variant of the gene that encodes the cholesterol-carrying apolipoprotein E as an Alzheimer's risk factor. Exactly how that variant, known as *ApoE4*, predisposes someone to the disease is not well understood, but since then several studies have also pointed to a link between cholesterol and Alzheimer's.



Alzheimer's risk? Cholesterol esters, such as those stored in the granules (red) of these Chinese hamster ovary cells, may foster Aβ production.

CREDIT: DORA KOVACS/GENETICS AND AGING RESEARCH UNIT (MASSACHUSETTS GENERAL HOSPITAL)

Two of the most intriguing are epidemiological studies that appeared last year. In these studies, researchers examined whether statins, which are taken by millions of people, influence the risk of getting Alzheimer's. "Since patients have been taking statins for years now, we thought we might be able to see an effect if it were present," says Benjamin Wolozin of Loyola University Medical Center in Maywood, Illinois, who led one of the studies.

The studies used different statistical designs and focused on different populations. Wolozin's team gathered data from patient records in two hospitals in Illinois and one in Arizona. Meanwhile, Herschel Jick of Boston University School of Medicine, David Drachman of the University of Massachusetts Medical School in Worcester, and their colleagues obtained data from the U.K.'s General Practice Research Database, a compendium of demographic and medical information from 3 million U.K. residents. Even so, the teams' conclusions were strikingly similar, Wolozin says: "The prevalence of Alzheimer's disease in people taking statins was about 70% lower" than in controls.

But Drachman is not sure that the effect was due primarily to the statins' cholesterol-lowering action. His team looked at the effects of other cholesterol-lowering drugs—and they did not reduce the risk of dementia. "The issue," Drachman says, "is what do the statins do that the other drugs don't do?" As one possibility, he points out that statins increase the activity of an enzyme called nitric oxide synthase in the blood vessel linings and decrease the activity of another protein called endothelin-1. As a result, they improve the function of small blood vessels and increase blood flow to the brain.

Other research with both cultured cells and animals, however, supports the premise that statins protect against Alzheimer's because they block cholesterol synthesis. In the mid-1990s, Sparks and his colleagues found that rabbits fed a high-cholesterol diet developed plaques and other signs of Alzheimer's pathology in their brains. The next question, says Sparks, now at the Sun Health Research Institute, was "Can we make this go away?" They could. Switching the rabbits to their normal low-cholesterol diet reduced the number of plaques. And even rabbits that gorged on a high-cholesterol diet developed far fewer plaques if they were also given probucol, a nonstatin cholesterol-lowering drug.

Clues to just how excess cholesterol might spur amyloid plaque formation came a few years later in studies of brain neurons in culture. In the past few years, several teams have shown that adding cholesterol to neurons makes them churn out more of the plaques' active ingredient: Aβ. Conversely, statins, as well as chemicals that extract cholesterol from the cell membrane, decrease formation of the peptide.

Neurons in culture are a far cry from

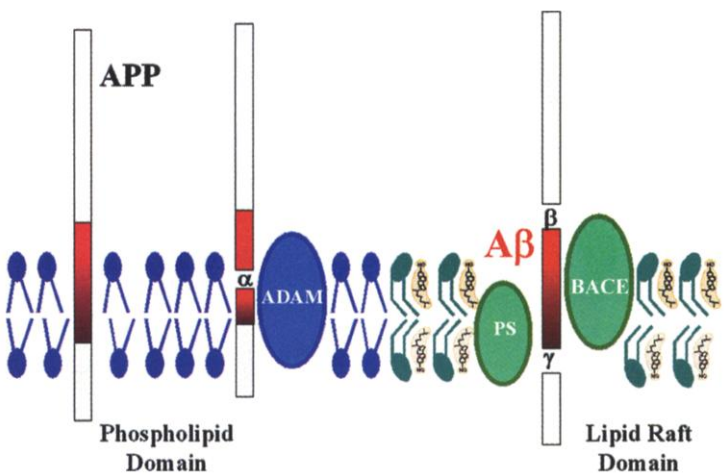
those in the human brain, but other work shows that cholesterol-lowering drugs also minimize Aβ production in the brains of living animals. Sparks previously demonstrated this in rabbits, and earlier this year, a team led by Konrad Beyreuther and Tobias Hartmann of the University of Heidelberg, Germany, found that simvastatin lowers Aβ levels in the brains and cerebral spinal cords of guinea pigs. And in as-yet-unpublished work, Larry Refolo, Karen Duff, and their colleagues at the Nathan S. Kline Institute for Psychiatric Research in Orangeburg, New Jersey, showed that an experimental cholesterol-lowering drug reduces production of the peptide in the brains of genetically engineered mice that develop plaques much like those in human Alzheimer's.

An indication that something similar might happen in humans comes from Mount Sinai's Buxbaum, Lawrence Friedhoff of Andrx Corp. in Hackensack, New Jersey, and their colleagues, who found that clinical doses of lovastatin reduce Aβ levels in the blood of human patients in a dose-dependent manner. The researchers were unable to see how the drug affects Aβ production in the patients' brains, but Buxbaum says that because lovastatin penetrates the brain, it's possible that it lowers Aβ production there, too.

Work with cultured cells is providing clues to how cholesterol-lowering drugs reduce production of Aβ. Cells produce the peptide by clipping it out of a larger protein called APP (for β-amyloid precursor protein), with the aid of two enzymes, known as the β- and γ-secretases. But APP is also cut by a third enzyme, the so-called α-secretase. Because this enzyme breaks APP within the Aβ segment, it prevents production of the neurotoxic peptide. Results reported in two papers in the 8 May issue of the *Proceedings of the National Academy of Sciences* (*PNAS*)—one from Beyreuther, Hartmann, and their colleagues and the other from a team led by Falk Fahrenholz of Johannes Gutenberg University in Mainz, Germany—suggest that cholesterol-lowering treatments inhibit Aβ formation by shifting the balance of activities of these enzymes to favor the α-secretase.

Fahrenholz and his colleagues found that the statin they used increased production of an α-secretase called ADAM10, but he notes that other effects on membrane biochemistry may have also contributed to the shift. And the Heidelberg team's *PNAS* paper suggests that cholesterol reduction decreases β-secretase activity, although Hartmann says that more recent work suggests that it decreases γ-secretase activity as well. The exact cause of the altered enzyme function is unclear, however. As Duff points out, "we know cholesterol affects amyloid load, but we don't know how."

One possibility is that changes in cholesterol content affect the activity of the APP-cleaving enzymes by altering their physiological milieu. Lipids and proteins aren't evenly distributed in cell membranes. For example, there's some evidence that APP and the β- and γ-secretases are located together in cholesterol-rich areas of the membrane known as "rafts." So removing cholesterol may disrupt that association, while at the same time making it easier for α-secretase, which prefers an environment rich in a different lipid called sphingomyelin, to access APP.



Environmental factor. APP may be more susceptible to an α-secretase (ADAM) in phospholipid-rich areas of the cell membrane, while the Aβ-producing β- and γ-secretases (PS and BACE) may have greater access in the cholesterol-rich rafts.

Yet another clue about cholesterol's relationship to Aβ comes from Dora Kovacs, Luigi Puglielli, and their colleagues at Massachusetts General Hospital in Boston, who made an intriguing observation about a possible role for an enzyme called acyl-coenzyme A: cholesterol acetyltransferase (ACAT). When cholesterol levels in the membrane get too high, ACAT removes the excess and adds on an acyl group, thus forming a cholesterol ester, which is stored in granules inside the cell.

Working with cells with mutations that either increase or decrease the formation of cholesterol esters, the Kovacs team showed that Aβ production correlates not with total cellular cholesterol but with cholesterol ester levels. Consistent with that, the Mass General workers also found that compounds that inhibit ACAT, and thus cholesterol esterification, also inhibit Aβ release.

The researchers, who describe their results in the October issue of *Nature Cell Biology*, do not yet know how high cholesterol ester levels boost Aβ production. In fact, Kovacs says, her team was "definitely surprised" by the result. It doesn't easily fit in with the fact that APP and the three secretases are found in the cell membrane, where it would be difficult for them to interact with granules. More work will clearly be needed to sort this out. But meanwhile, Kovacs says, "the important thing is that this means that inhibitors of ACAT could theoretically be used as inhibitors of Aβ production" and thus as Alzheimer's drugs.

Wolozin, for one, welcomes that idea, calling the Kovacs team's findings "really important." He and others point out that statins, which block a very early step in cholesterol synthesis, may not be ideal for long-term use for Alzheimer's prevention. The drugs have been associated with sometimes dangerous side effects. A few months ago, the Bayer Group of Leverkusen, Germany, recalled its statin, known as cerivastatin or Baycol, because several people died from a condition called rhabdomyolysis, in which the muscles break down. That problem may have been linked to the simultaneous use of another, nonstatin cholesterol-lowering drug called gemfibrozil, but statins alone can also cause liver damage in some people.

Still, researchers are eager to see how the drugs fare in the trials now under way or planned. It will be at least a year before results of the Arizona trial are in, and the ADCS study hasn't begun yet. Both trials will be conducted on patients who have early symptoms of Alzheimer's and therefore have already suffered considerable brain degeneration. This may make it more difficult to see treatment benefits.

That should not be a problem, however, with the Prospective Study of Pravastatin in Elderly at Risk (PROSPER) now being conducted on more than 5000 people in Scotland, Ireland, and the Netherlands. In addition to seeing how the statin affects the cardiovascular health of these people, researchers will also follow its effects on their cognitive function. Results are expected next year. If the statins or other cholesterol-lowering drugs do benefit patients, we can conclude that lowering cholesterol helps the mind as well as the heart. **–JEAN MARX**

CREDIT: B. WOLOZIN, *PNAS* 98, 5371 (2001)