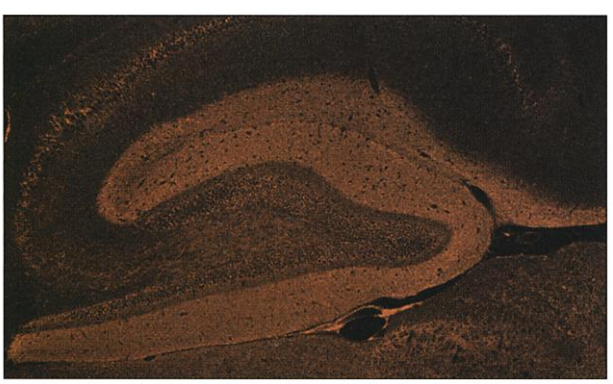
fault in other neurological diseases as well. Alzheimer's disease is defined in part by protein tangles inside the cell similar to those modeled in the current study. But other protein clumps, amyloid plaques outside neurons, have received more attention lately (see following story). Kopito says it's possible an overloaded UPS or similar mechanism could allow plaques to form. He also suspects UPS overload in bovine spongiform encephalopathy, or "mad cow disease," and its human cousin, Creutzfeldt-Jakob disease, which are both characterized by clumps of abnormal protein fragments. If so, says Kopito, "this could be an explanation" for how these mysterious diseases kill neurons.

–LAURA HELMUTH

NEUROBIOLOGY

New Clue to the Cause of Alzheimer's

Alzheimer's disease sneaks up on its victims, robbing them first of short-term memory and then ultimately of all ability to think and reason. Like several other neurological diseases, Alzheimer's seems to be caused by abnormal protein deposits accumulating in the brain (see previous story). In Alzheimer's, the prime suspect is a small protein called amyloid beta (Aβ), which is a major component of the pathological plaques that stud the patients' brains. But what causes that protein to accumulate?



Alzheimer's suspect. The red staining shows the distribution of neprilysin in the normal mouse brain.

Most Alzheimer's researchers have focused on the enzymes that free Aβ from its precursor protein (*Science*, 29 September 2000, p. 2296). By releasing too much Aβ, overactive enzymes could lead to abnormal Aβ deposition in the brain. Recently, however, researchers have been approaching the problem from a different direction: looking for enzymes that degrade the peptide. If the enzymes are underactive, the result could also be Aβ buildup. "It's just as important to find the [Aβ] degradation pathway as the synthesis pathway," says Rudolph Tanzi, an Alzheimer's researcher at Massachusetts General Hospital in Boston.

On page 1550, a team led by Takaomi Saido of the RIKEN Brain Science Institute in Saitama, Japan, now provides direct evidence in mice that a protease called neprilysin could be a natural Aβ-degrading enzyme. "It might play an important role in clearing Aβ in the brain," says Alzheimer's researcher Sangram Sisodia of the University of Chicago Pritzker School of Medicine. But he and others caution that more work will be needed to confirm that neprilysin does indeed break down Aβ. Neprilysin is not the only candidate for that job, however.

Last year, Dennis Selkoe's team at Harvard Medical School in Boston showed that a neuronal protein called insulin-degrading enzyme can break down the peptide in lab cultures. If a deficiency of either—or both—of these enzymes turns out to contribute to Alzheimer's, the enzymes could provide new targets for drugs to prevent or treat the disease, which afflicts 4 million people in the United States alone.

Saido's team identified neprilysin as a possible Aβ-degrading enzyme about a year ago. In that work, the team injected mouse brains with Aβ and also with a series of specific protease inhibitors to see which would reduce the breakdown of the peptide. This led the researchers to neprilysin and three related protein-destroying enzymes. Because neprilysin had the greatest activity against Aβ in test tube studies, the scientists collaborated with Craig Gerard's team at Harvard Medical School, which had knocked out the neprilysin gene in mice, to see how that affected the animals' ability to degrade the peptide.

When injected into the brains of normal animals, Aβ is broken down within about 30 minutes. But in the knockout mice, the researchers found, almost all of the peptide persisted. By crossing knockout mice with normal animals, the team produced mice that have just one active copy of the neprilysin gene. These animals yielded intermediate results: More of the injected Aβ persisted than in normal animals, but less than in the complete knockouts. That's important, Saido says, because it "indicates that even partial reduction of neprilysin activity, which could be caused by aging, will elevate Aβ and thus cause Alzheimer's."

The Saido team also found that natural Aβ levels in the knockout mice were highest in brain regions, such as the hippocampus and cortex, where Alzheimer's plaques are most prominent. This and recent findings from Patrick McGeer and his colleagues at the University of British Columbia in Vancouver are consistent with the possibility that neprilysin deficiency could contribute to Alzheimer's, says Saido. When McGeer's group analyzed neprilysin levels in the brains of patients who had died of the disease, they found the lowest levels in the high-plaque regions. "If you have adequate amounts of neprilysin, you never accumulate Aβ," McGeer concludes.

Despite the biochemical evidence suggesting that neprilysin deficiency could lead to Alzheimer's, to clinch the case researchers are waiting for two additional findings. One would be the demonstration that neprilysin deficiency increases plaque formation in an Alzheimer's mouse model—an experiment that Saido describes as the "top priority." The other is genetic evidence linking the neprilysin gene to human Alzheimer's.

Tanzi's group at Harvard has found hints of such a genetic linkage between human Alzheimer's and the region on chromosome 3 where the neprilysin gene is located. It was just short of statistical significance, however, and he hasn't published the work. But a neprilysin deficiency could be caused by a defect in the machinery needed for expressing the gene, as well as in the gene itself, Saido speculates.

Meanwhile, Selkoe and his colleagues are following up on the insulin-degrading enzyme. Among other experiments, they are knocking out the gene in mice to see whether that alters Aβ handling in the brain. If at least one of these enzymes proves to be a bona fide Aβ-degrading enzyme in the brain, Alzheimer's researchers will have an important new line of investigation to pursue in their efforts to tame this devastating disease.

–JEAN MARX

SOLID STATE PHYSICS

Rubbery Liquid Crystal Gives Lasers a Stretch

You won't find it in gumball machines, but Heino Finkelmann's stretchable laser may be the cutest example of elasticity since Silly Putty. Finkelmann, a physical chemist at the University of Freiburg, Germany, created a new type of artificial rubber with the light-altering properties of a liquid crystal display. Then, colleagues at Kent State University in Kent, Ohio, showed that it could be used as a new type of laser—one that emits light without mirrors or a cavity and that changes its wavelength when pulled like taffy.

Behind the fun lies serious physics. Finkelmann's rubber is a photonic bandgap material, one that can block light in a controlled way. Such materials are important as tiny light guides in the world of optical communications, but they are expensive and tricky to en-

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