Unveiling the tau of neurodegeneration

A protein called tau maintains the structure and function of neurons, the basic cells of the brain and nervous system. Scientists have long thought that disaster would strike anyone whose tau was disrupted. This month, proof arrives that they are right.

Three new studies show that mutations in the gene that encodes the tau protein underlie some forms of frontotemporal dementia (FTD). Though less common than Alzheimer's disease, FTD is one of the most prevalent forms of dementia, accounting for 5 to 10 percent of cases.

In people carrying any of these newly described mutations, neurological degeneration sets in sometime after age 48, the researchers report. Those suffering from the resulting dementia can exhibit diminished speech, tremors similar to those seen in Parkinson's disease, and behavior that resembles schizophrenia.

"Possibly this breakthrough in tau will lead to better understanding of the protein and how it contributes to the death of nerve cells," says Marcelle Morrison-Bogorad, an associate director of the National Institute on Aging in Bethesda, Md. "It's the first time tau has been fingered as the culprit in any genetic disease. It's a protein that's been left out in the cold too long."

Nonetheless, tau is no stranger to neuroscientists. This protein maintains the structure of microtubules, intracellular proteins that act as miniature train tracks within neurons. Microtubules usher nutrients and other substances back and forth to keep the cell alive and running smoothly.

The tau protein appears to function much like railroad ties, binding the microtubule tracks together and making the trains run on time, Morrison-Bogorad says. The microtubules are then able to deliver goods to the all-important ends of the neuron's long, filamentous structures that can carry signals along nerve channels to distant parts of the body.

If the gene encoding tau has a mutation, this system can be disrupted and the neuron dies, three research teams find.

It could be that the proteins produced by the mutated gene don't keep the microtubules together, says neurobiologist Michael Hutton of the Mayo Clinic in Jacksonville, Fla., who coauthored one of the reports. Or, he suggests, the mutations may leave tau protein with nothing to do, and its accumulations may somehow lead to cell death. "There may be too much unbound tau around," he says, "and that's bad news."

Scientists are suspicious of extra tau because the spaghetti-like tangles found in the brains of people with Alzheimer's disease are loaded with the accumulated protein. However, they haven't been shown to have mutations in the *tau* gene. On the other hand, people with FTD do not show the amyloid plaque buildup that characterizes Alzheimer's disease.

Whereas the role of tau in Alzheimer's disease remains blurry, the protein is clearly problematic in FTD. In the June 3 ANNALS OF NEUROLOGY, researchers at the Veterans Affairs Puget Sound Health Care System in Seattle report that they analyzed nine variations in the gene, on chromosome 17, that encodes tau protein. Eight of them appeared to be innocuous, showing up in healthy people as well as in those having FTD. The ninth, however, only surfaced in the subjects with FTD. What's more, this mutation occurred in DNA that encodes the part of tau protein that binds to microtubules.

Neurobiologist Maria Grazia Spillantini of the University of Cambridge in England, who has worked on tau for a decade, and her colleagues in Britain and the United States have discovered that the *tau* gene repeats—sometimes three times and sometimes four times—a precise sequence encoding 31 amino acids. When the ratio of repeats gets overloaded toward too many quadruple repeats, the protein somehow proceeds to get tangled up in the neuron, she says.

Quite possibly, protein segments encoded by triple repeats bind to different sites on the microtubules than do segments encoded by quadruple repeats, she and her colleagues say. Thus, a changed ratio of repeats could be enough to derail the microtubule train. Their report appears in the June 23 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Hutton, working with other researchers in Europe and Australia, identified six mutations in the *tau* gene among several extended families with members having FTD. Of 565 people in families with no cases of the dementia, none showed any of the six mutations, the scientists report in the June 18 NATURE.

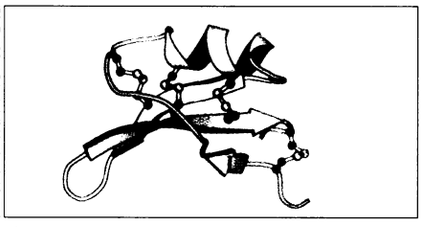
"This series of papers is going to be a tremendous impetus in jump-starting research into tau," Morrison-Bogorad says. "There have been faithful tau followers for many years. This will increase their ranks." —*N. Seppa*

Protein's shape may give extra-sugary taste

"Short and sweet" best describes brazzein, a protein found in a West African fruit. Just 54 amino acids long and 2,000 times sweeter than sugar, brazzein is one of only six proteins known to taste sugary to humans and other primates.

Now, researchers at the University of Wisconsin-Madison have determined brazzein's three-dimensional structure, a finding that may eventually shed light on what gives these proteins their flavor. Presumably, it is their shape that allows them to bind to sweet taste receptors on the tongue. Scientists already know the structures of two other sweet proteins, thaumatin and monellin (SN: 5/10/97, p. 284), but they don't seem to resemble each other.

Brazzein doesn't appear to resemble either thaumatin or monellin. In fact, its structure has more in common with some scorpion toxins and plant defense proteins. That similarity "doesn't really tell us much" about why brazzein tastes sweet, says Wisconsin's Göran B. Hellekant.



J.E. Caldwell *et al.*/*Nat. Struct. Biol.*

A computer model of brazzein, a sweet protein.

It may, however, say something about how the protein evolved, he notes. Brazzein's resemblance to proteins that plants use to defend themselves against microbes suggests that its precursor once had the same function in the fruit. Through mutations, the original protein may have lost its defense capability and become sweet, Hellekant speculates. He, John L. Markley, and their colleagues report the findings in the June NATURE STRUCTURAL BIOLOGY.

"This is an important piece of work in the context of protein sweeteners," says Joseph Brand, associate director of the Monell Chemical Senses Center in Philadelphia. Comparing the structure of brazzein, which is smaller and more rigid, to those of thaumatin and monellin may allow researchers to understand how all three bind to sweet taste receptors, he adds.

Brazzein's rigidity originates from four links called disulfide bridges that lock in the protein's three-dimensional shape. The bridges make brazzein very stable to heat, a property the food industry finds attractive. Once unfolded, brazzein loses its flavor, as do the other sweet proteins. The researchers next intend to shuffle the protein's sections to see how their arrangement affects the taste.

Hellekant envisions that the food industry could use brazzein as an additive like sugar or aspartame or, via genetic engineering, transfer it into fruits and vegetables. Because brazzein comes from a plant, *Pentadiplandra brazzeana* Baillon, it should be easier to incorporate into crops than aspartame, an artificial sweetener, he suggests.

African monkeys and apes find the intensely sweet fruit irresistible, Hellekant says. Perhaps one day, brazzein will make other foods just as tasty to humans. —*C. Wu*