Clue to Lou Gehrig's Disease Emerges

Amyotrophic lateral sclerosis (ALS), the neurodegenerative disease that killed baseball legend Lou Gehrig and slays about 1 in 1,000 people, has largely defied explanation. An inherited enzyme defect identified in 1993 accounts for only a few percent of the cases.

Now, researchers have evidence suggesting that many ALS cases, perhaps the majority, result from abnormal genetic instructions that leave the brain and spinal cord unable to sponge up glutamate, a potentially destructive amino acid. The resulting glutamate buildup presumably causes the disease's cardinal feature—the death of the nerve cells, or neurons, that control the body's muscles.

Neurons normally release small amounts of glutamate to signal neighboring cells. Yet because exposure to large quantities of this neurotransmitter can kill neurons, cell surface proteins known as glutamate transporters must quickly recycle the amino acid.

At last week's Society for Neuroscience meeting in Washington, D.C., Jeffrey D. Rothstein of Johns Hopkins University in Baltimore and his colleagues described a study of one glutamate transporter, EAAT2. When the researchers examined tissues from 20 people who had died of ALS, they found that 10 had frequently harbored mutations in the genetic instructions used to construct that crucial transporter.

To build proteins, cells normally use a gene's exons, its protein-coding regions, to create messenger RNA (mRNA) molecules. The protein-making equipment of cells reads these strands of mRNA to determine which amino acids to link together.

In their study of brain and spinal cord tissue from people who had died of ALS, Rothstein's group examined the mRNAs created from the gene for EAAT2. In half of the patients, the researchers found abnormal mRNAs. Some lacked a copy of one of the gene's exons. Others contained introns, non-protein-coding regions of the EAAT2 gene, in place of the gene's final exon. The scientists found that these mRNAs do not produce functional glutamate transporters.

To determine whether the mutant mRNAs were specific to ALS, Rothstein's group examined brain and spinal cord tissue from 24 people who had died of other neurodegenerative diseases or non-neurological causes. None of these tissues had the mutant mRNAs.

The mutant mRNAs and the resulting absence of EAAT2 may explain an earlier finding by Rothstein's group that ALS patients have problems clearing glutamate (SN: 3/26/94, p. 203).

"This is very exciting. It sounds like a substantial step forward in understanding the loss of glutamate transport. It helps strengthen the original finding," says Dennis W. Choi of Washington University in St. Louis.

The glutamate transporter EAAT2 is found only on glia, the support cells that surround neurons. Though nerve cells possess their own forms of glutamate transporters, EAAT2 appears to be the most effective glutamate sponge. Rothstein's group reported in the March NEURON that eliminating this glutamate transporter in rats triggers an ALS-like neurodegeneration that results in paralysis.

"These proteins are critical for the clearance of extracellular glutamate. If the proteins are not present, neurons die," says Rothstein.

Why are the mRNAs produced incorrectly? The EAAT2 gene may contain mutations, though researchers have not identified any so far. Rothstein also speculates that the abnormal mRNAs may result from mutations in a second gene, whose protein is involved in creating the mRNAs.

A defect in glutamate clearance might explain the rare, inherited form of ALS attributed to an abnormal version of an enzyme called superoxide dismutase (SOD). Rothstein's group has some evidence that the enzyme's actions alter EAAT2 proteins. "We don't know how the mutant SOD is toxic. It might injure the glutamate transporter," he says.

Cautioning that the group's results are preliminary, Rothstein says he and his colleagues plan to seek further proof that a shortage of glutamate transporters underlies many ALS cases.

Nonetheless, he remains hopeful that the identification of the mRNA mutations will lead to a test enabling physicians to diagnose ALS early in the disease process. Moreover, confirming that glutamate is the central player in neuron death from ALS would narrow the focus of researchers searching for potential therapies, says Rothstein. —*J. Travis*

Making antihydrogen atoms at Fermilab

Creating hydrogen is as straightforward as mixing together electrons and protons so that electrons wind up orbiting protons. Making antihydrogen is much tougher because the ingredients—positrons (the positively charged antimatter counterparts of electrons) and antiprotons (the negatively charged antimatter counterparts of protons)—are significantly trickier to obtain, store, and control (SN: 10/21/95, p. 268).

Not until last fall did physicists produce antihydrogen in the laboratory for the first time (SN: 1/13/96, p. 20). Now, a second team of researchers has reported creating antihydrogen atoms, which they generated in high-speed interactions between a beam of antiprotons and a jet of hydrogen gas.

David C. Christian of the Fermi National Accelerator Laboratory in Batavia, Ill., and his coworkers announced their initial findings last week, reporting the detection of seven antihydrogen atoms.

In both the earlier experiment at the European Laboratory for Particle Physics (CERN) in Geneva and the Fermilab experiment, researchers generated beams of antiprotons traveling at nearly the speed of light in an accelerator. Periodically, the circulating antiprotons would pass through a transverse jet of gas atoms. The CERN team used xenon for its jet, whereas the Fermilab group chose hydrogen.

Occasionally, an antiproton would pass close enough to a jet atom to give up a portion of its energy to create an electron and a positron. In even rarer instances, the newly created positron had a velocity close to that of an antiproton, so the position would get captured, creating a short-lived atom of antihydrogen.

Taking advantage of a more intense, higher-energy antiproton source than that at CERN, the Fermilab team expects to create and detect as many as five antimatter atoms per day once the accelerator is running optimally. "We anticipate detecting about 750 atoms of antihydrogen by next September," says Glenn D. Blanford of the Fermilab team.

Physicists would like eventually to use antihydrogen to check whether antimatter behaves in exactly the same way as ordinary matter. One crucial test involves a precise comparison of the wavelengths of light absorbed and emitted by these atoms.

However, the antiatoms created at CERN and Fermilab travel far too quickly and don't last long enough for researchers to measure their characteristics. Only when scientists can trap a large number of antihydrogen atoms can such investigations proceed. —*I. Peterson*