Natural sedatives linked to brain disorder

Natural tranquilizers may play a key role in the development of a brain disorder that strikes people with liver disease, according to a preliminary study. If confirmed, the finding may lead to more effective treatment of this potentially fatal disease, called hepatic encephalopathy.

The prevailing theory holds that high blood levels of ammonia, caused by a malfunctioning liver, lead to the symptoms of hepatic encephalopathy, which include drowsiness, memory loss, stupor and in some cases coma. But a report in the July 14 LANCET implicates mysterious natural substances that behave like benzodiazepine drugs such as Valium.

"The report raises the suggestion that patients with advanced liver disease could be accumulating a substance in their blood that makes them confused by simulating the action of Valium," says study coauthor Kevin D. Mullen of Case Western Reserve University in Cleveland.

Mullen's previous research had revealed unidentified, benzodiazepine-like substances in the cerebrospinal fluid of rabbits with hepatic encephalopathy. Mullen knew the rabbits weren't popping Valium, and he knew high doses of benzodiazepine drugs could cause stupor and loss of consciousness. He began to search for similar compounds in the body fluids of people with liver disease who showed signs of encephalopathy.

Now Mullen and his colleagues report that eight people hospitalized with liver failure and severe encephalopathy show evidence of benzodiazepine-like compounds in their cerebrospinal fluid at much higher levels than eight control patients hospitalized for other conditions. The researchers excluded study volunteers who said they had taken a synthetic benzodiazepine during the past three months. They also scrutinized medical records and talked with volunteers' physicians to make sure the participants hadn't taken such synthetic drugs.

The team then turned to people with varying stages of hepatic encephalopathy, taking blood samples from 23 patients and urine samples from 36. Indirect tests indicated that these samples contained significantly higher levels of benzodiazepine-like substances than samples from controls with healthy livers. People with the highest levels of the substances seemed to have the most severe symptoms of hepatic encephalopathy, Mullen adds.

The scientists don't know where the puzzling substances originate, but they hypothesize that people with liver failure may somehow accumulate high levels of the natural benzodiazepine compounds present in foods. Some foods, such as wheat and potatoes, contain minuscule amounts of natural benzodiazepines, but they do not cause sedative effects in healthy people, Mullen notes. He speculates that people with liver disease may store up dietary benzodiazepines until the compounds reach a level that causes drowsiness, stupor or even coma.

The new report bolsters previous research suggesting that drugs that block benzodiazepine receptors in the brain might reverse symptoms of hepatic encephalopathy. European researchers have reported that one such drug can rouse comatose liver-disease patients. U.S. scientists have yet to test the experimental drug, notes Anthony S. Basile of the National Institute of Diabetes and Digestive and Kidney Diseases. Basile's own unpublished research has identified two specific benzodiazepines in the brain tissue of people who died of hepatic encephalopathy.

Mullen and others say further research must prove the link between naturally occurring benzodiazepines and the symptoms of liver encephalopathy. Without such proof, many continue to back the ammonia theory. Leslie Zieve, a liver specialist at the University of Minnesota in Minneapolis, calls Mullen's findings intriguing and worthy of further attention, but says he still believes ammonia is the major culprit in this brain disorder.

– K.A. Fackelmann

Protons and antiprotons held in the balance

Created by slamming speeding protons into a metal target, antiprotons begin their lives with far too much energy to allow precise measurements of their properties. But by slowing down these elusive particles – the negatively charged, antimatter counterparts of protons – and holding them for extended periods of time in an electromagnetic trap, physicists can begin probing their characteristics.

A research team led by Gerald Gabrielse of Harvard University has now managed to cool antiprotons to a temperature of 4 kelvins and hold them in a trap for several months. The feat enabled the scientists to demonstrate that a proton and an antiproton have the same mass with a precision of four parts in 100 million – a thousandfold improvement over previous measurements of the proton-antiproton mass ratio.

"That's a big, big increase in precision," Gabrielse says. "One doesn't get to do that very often, and we're hoping to go up by another factor of 10 or perhaps 100 in the future." The achievement also opens the possibility of measuring various other properties of antimatter with sufficient precision to test the validity of present-day theories of the structure of matter.

To make their unprecedented measurements, Gabrielse and his collaborators at the University of Washington in Seattle and the University of Mainz in West Germany overcame a number of significant obstacles, including the antiproton's quick annihilation in any encounter with ordinary matter.

Produced in a low-energy proton accelerator at the CERN laboratory in Geneva, Switzerland, bursts of antiprotons emerge with a kinetic energy of 6 million electron-volts, traveling at a significant fraction of the speed of light. Most of the antiprotons pass through an aluminum plate, which decelerates a fraction of the particles enough to allow their capture in a specially designed electromagnetic trap consisting of a stack of five cylindrical electrodes.

Awaiting the trapped antiprotons is a cloud of electrons already cooled to 4 kelvins. As the antiprotons repeatedly pass through this cloud, they gradually lose energy by interacting with the electrons. They eventually reach an average kinetic energy of less than 1 milli-electron-volt, moving at the subatomic equivalent of a snail's pace.

It's like a car plowing through a tunnel full of table-tennis balls, Gabrielse says. "You need lots of collisions, but after a while you really do lose energy. And it turns out to be incredibly effective for cooling."

Indeed, the cooling is so effective and the trap so empty of stray gas molecules that antiprotons can stay trapped for at least 15 weeks. "Our results are consistent with no losses at all over several months," Gabrielse says.

To compare the proton and antiproton masses, the researchers measure the frequencies at which protons, and then antiprotons, orbit around magnetic field lines within the trap. The value of this so-called cyclotron frequency depends on a particle's charge-to-mass ratio. The resulting proton-antiproton mass measurement agrees with the theoretical prediction that particles and their antiparticles must have identical masses.

Gabrielse and his co-workers hope to achieve even greater precision in future measurements, perhaps by reducing the number of antiprotons stored in a trap or by moving the apparatus away from its electromagnetically noisy surroundings at CERN.

"We've concentrated all of our efforts in the last few years on slowing and cooling antiprotons by more than 10 orders of magnitude in energy, and that was a rather large challenge," Gabrielse says. "Now, we and others are beginning to think about how we can use it. We've opened up a new low-energy frontier, and we don't know exactly where it's all going to take us."

– I. Peterson