Faulty protein repair spurs mouse seizures

People don't normally throw away their silverware after a single meal. It's usually cheaper to wash and reuse the utensils than to buy new ones.

Similarly, cells may sometimes do better to repair partially damaged proteins than waste a fair amount of energy synthesizing replacements. In test-tube experiments, scientists had identified a few repair mechanisms that cells may employ, but they had obtained little information on whether animals actually depend on such molecular restoration.

Dramatic proof that they do is now at hand. Investigators who created mice bereft of an enzyme implicated in protein repair have discovered that the seemingly healthy rodents suffer fatal seizures within a month or two of birth.

The enzyme's absence "has rather dire consequences. It's an exciting development and emphasizes the importance of this repair pathway," says Earl R. Stadtman, a protein repair investigator at the National Heart, Lung, and Blood Institute in Bethesda, Md.

Compared to the crush of scientists examining how cells fix DNA damage, few researchers have focused on the natural deterioration of proteins as cells age. In recent years, however, some scientists have championed a theory of aging that blames the gradual accumulation of damaged proteins, many of them generated by interactions with highly reactive, oxygen-bearing molecules known as free radicals (SN: 5/18/96, p. 311).

Other forms of protein damage also occur naturally, including spontaneous degradation of amino acids such as asparagine and aspartic acid. Such damage involves "a shuffling around of atoms within the molecules. It can grossly affect the whole structure of a protein," notes Edward Kim of the University of California, San Francisco.

Scientists had found an enzyme called both L-isoapartyl (D-aspartate) *O*-methyltransferase and PCMT-1 that in test tubes could heal proteins with this type of amino acid injury. However, they didn't know whether cells use the enzyme in this way or simply junk damaged proteins and make new ones.

Kim and his colleagues genetically engineered mice to lack PCMT-1. Though significantly smaller than normal, the rodents seemed healthy. After several weeks, however, the situation changed. When researchers left the lab for the evening, or even a few hours, they would often find a dead mouse when they returned.

Autopsies revealed no obvious abnormalities, so the investigators began videotaping the mice around the clock. They discovered that the animals suffered fatal seizures. Their muscles would begin to twitch, and after several minutes they would run around or jump for 15 to 20 seconds. Finally, they would fall on their sides and stop breathing.

Since the seizures suggested abnormal brain activity and PCMT-1 is most abundant in the brain, the scientists examined cells there for damaged proteins. They found plenty. About 6 percent of the proteins inside the cells were damaged, they estimate in the June 10 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES. Normally, less than 1 percent are faulty, says Kim.

How the absence of PCMT-1 generates seizures remains unclear, though Kim and his colleagues speculate that the accumulation of damaged proteins may interfere with the metabolism of glutamate, a crucial neurotransmitter.

The question of PCMT-1's relevance to aging remains open. "The premature death of the mice precludes a test of [the enzyme's] role in aging," notes George M. Martin, a gerontologist at the University of Washington in Seattle.

Kim and his colleagues agree, and they now plan to test the aging theory by generating mice that make PCMT-1 in the brain but nowhere else. That should prevent the seizures and may allow the mice to live long enough for other organs to exhibit difficulty in dealing with damaged proteins, says Kim. —*J. Travis*

Social sense may heed uneven inheritance

The television series *Men Behaving Badly* features a couple of socially inept, responsibility-challenged bachelors imported from a British situation comedy. Scientists now report that real-life British "women behaving badly"—at least those afflicted with a particular inherited disorder—have provided clues to the genetics of social intelligence.

The X chromosome apparently contains a still-unidentified gene that contributes to one's ability to gauge others' social reactions and to inhibit impulsive acts, contends psychiatrist David H. Skuse of the Institute of Child Health in London and his coworkers. The suspected gene appears to influence social thinking in different ways, depending on the gene's parental source.

"We're going to continue hunting for what I suspect is a single gene with many actions that in some way influence social cognition," Skuse says. That gene undoubtedly interacts with others on different chromosomes, he adds.

Women typically have two X chromosomes, one inherited from each parent; men receive an X chromosome from their mother and a Y chromosome from their father. Skuse and his colleagues studied 80 females age 6 to 25 who lack all or part of one X chromosome.

This condition, known as Turner's syndrome, affects 1 in 2,500 females. It is characterized by short stature and stunted sexual development at puberty. Problems with social adjustment often occur, although scores on intelligence tests fall within the normal range.

The researchers divided their volunteers into two groups: 55 with a complete X chromosome inherited from their mother and 25 with an undamaged X chromosome from their father.

Marked social difficulties and academic failure occurred far more often in the group with a maternally inherited X chromosome, the researchers report in the June 12 NATURE. These females also scored lower on a test of word knowledge and reading comprehension and on a parent-completed questionnaire about the extent to which they displayed social insight and adeptness.

Both groups of volunteers achieved lower scores on those measures than previously established standards for females with two complete X chromosomes, the researchers note.

Maternal-X females scored particularly poorly on a "behavioral inhibition" task that assessed their ability to suppress familiar responses. Volunteers saw a random series of the numbers 1 and 2 and had to say "one" in response to 2 and "two" in response to 1. Paternal-X females did as well on this task as females with both X chromosomes. Males typically score lower than females on behavioral inhibition tests of this type.

Finally, Skuse's team found that another eight Turner's syndrome volunteers, each lacking much of the short arm of the paternally inherited X chromosome, performed as well on social and verbal tests as the other group of paternal-X females. This suggests that the gene implicated in social intelligence lies elsewhere on that chromosome, Skuse holds.

His report represents the first evidence that a gene on the X chromosome works differently depending on which parent it's inherited from, according to an accompanying commentary by Peter McGuffin and Jane Scourfield of the University of Wales College of Medicine in Cardiff.

Two other provocative possibilities emerge from these results, Skuse remarks. First, the existence of a gene on the maternally inherited X chromosome that disturbs social skills may explain why males prove more vulnerable to some developmental disorders, such as autism and attention-deficit disorder. Second, this X-linked gene may contribute to sex differences in aggressiveness and social skill often attributed solely to cultural influences and child rearing. —*B. Bower*