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Neuronal "Traffic Jam" Marks Early Alzheimers Disease

Early Alzheimer's disease may be precipitated by a "traffic jam" within neurons that causes swelling and prevents proper transport of proteins and structures in the cells, according to new studies by Howard Hughes Medical Institute researchers.

In mouse models of Alzheimer's disease and in human brain samples from people with the disease, researchers observed a characteristic breakdown in neurons that appears to prevent the normal movement of critical proteins to the communications centers of the nerve cells. In a vicious cycle, the traffic jam also could increase production of an abnormal protein that clogs neurons, leading to their failure and eventual death.

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— Lawrence S. B. Goldstein

The researchers said their findings could provide information that might be used to develop drugs to preserve the molecular transport system and thus the viability of brain cells otherwise lost in Alzheimer's. The findings also could ultimately lead to distinctive markers of early Alzheimer's disease that could be used in early diagnostic tests for the disorder, they said.

The research team led by Lawrence S. B. Goldstein, a Howard Hughes Medical Institute investigator at the University of California, San Diego (UCSD), reported their findings in the February 25, 2005, issue of the journal *Science*. Goldstein and his colleagues at UCSD collaborated on the studies with a researcher at the Albert Einstein College of Medicine.

According to Goldstein, there has been evidence that late-stage Alzheimer's disease involves a failure of the machinery that transports proteins within neurons. In studies with fruit flies, Goldstein and others had observed that overexpression of the gene for a key protein that underlies Alzheimer's

pathology, called beta amyloid precursor protein (beta-APP), triggers defects in axonal transport. A defective version of beta-APP is cleaved to form an aberrant form of amyloid beta (A-beta) peptide that makes up the plaques that surround the neurons of people with Alzheimer's disease.

“With the findings from fruit flies as our guide, we decided to look at mouse models of Alzheimer's disease early in their life, before plaque formation, to see if we could detect early evidence of abnormal axonal transport,” said Goldstein. The researchers used mice that had been engineered to have an abnormal production of human A-beta peptide that produced Alzheimer's-like plaques and subsequent neural degeneration.

The scientists' analyses of the neurons in those mice revealed clear defects, said Goldstein. “What we saw quite early in the life of those animals—well before any plaque deposition—were obvious axonal defects,” said Goldstein. “We saw large swellings in their axons. And when we looked at those swellings using electron microscopy and biochemical markers, they looked just like the axonal transport blockages we saw in fruit flies.” Detailed studies of the neurons revealed what Goldstein termed a “traffic jam” of transport-related proteins, organelles and sac-like vesicles that are the cargo-carriers for cellular proteins.

Goldstein and his colleagues also examined brain sections taken at autopsy from humans with different stages of Alzheimer's disease. They detected the same kinds of swelling in those samples that they had seen in the mice. “This was a small, initial neuropathological study, but we believe that it is significant,” said Goldstein. “We found in the early cases a very strong, statistically meaningful swelling in the neurons.”

The researchers tested whether they could enhance the pathology they observed in the mice and humans by reducing the levels of a key transport protein, kinesin-1, the cell's principal molecular motor for transporting proteins. “We made a modest reduction in the level of a motor protein called kinesin-1 in the mice, and we got a considerable increase in plaque production and plaque deposition,” said Goldstein. “This makes it clear there is some mechanistic connection between the transport deficit and plaque deposition.

“So, our hypothesis is that in familial Alzheimer's disease—or in disorders such as Down syndrome where beta-APP is overexpressed—those defects cause early failure in cellular transport,” he said. “And those failures then stimulate further production of A-beta peptide, which may further poison the machinery.”

Goldstein theorized that Alzheimer's disease might develop spontaneously in people without an overt genetic defect, as the transport machinery in their neurons breaks down with age. “A person could have a predisposition to the disease, or it could just be that as time progresses, one person could by chance accumulate these blockages more than another,” said Goldstein. “And randomly, some people would accumulate more than others, enough to cross a critical threshold and tip the scale toward disease.”

Goldstein emphasized that any application of these findings to potential diagnostic tests or new therapies remains speculative at this time. “However, if tracers could be developed that would reflect transport function, there could be imaging methods that might be helpful for diagnosis,” he said. “And, if these findings continue to hold for humans, the transport machinery could be a target for drugs to preserve that machinery.”

The researchers plan to continue their exploration of the transport machinery's involvement in Alzheimer's pathology by using human embryonic stem cells to differentiate into neurons in culture. Their goal is to alter those neurons genetically by introducing mutations known to cause Alzheimer's disease in people, to then test for transport defects, and then study whether those defects produce pathology similar to that seen in Alzheimer's. One of the questions they will also ask is whether amyloid plaques poison the transport machinery. If the experiments do, indeed, confirm the predictions of the transport hypothesis, then neuronal cultures could prove valuable in testing diagnostic and therapeutic approaches, said Goldstein.

The researchers are also analyzing more brain tissue samples from humans with Alzheimer's disease, to confirm their findings of the early transport defects and their effects on neuronal death.