

Alzheimer's Protein Jams Mitochondria of Affected Cells

by Stephen Bradt

Opening a new front in the battle against Alzheimer's disease, scientists at the School have found that a protein long associated with the disease inflicts grave damage in a previously unimagined way: It seals off mitochondria in affected neurons, resulting in an "energy crisis" and buildup of toxins that causes cells to die. This pathway, the first specific biochemical explanation for pathologies associated with Alzheimer's, was detailed in the April 14 issue of the *Journal of Cell Biology*.

While the normal function of the amyloid precursor protein (APP) remains unknown, senior author **Dr. Narayan G. Avadhani** and his colleagues have determined that a mere 50-amino-acid stretch of the protein wreaks havoc by essentially starving mitochondria and the cells they nourish.

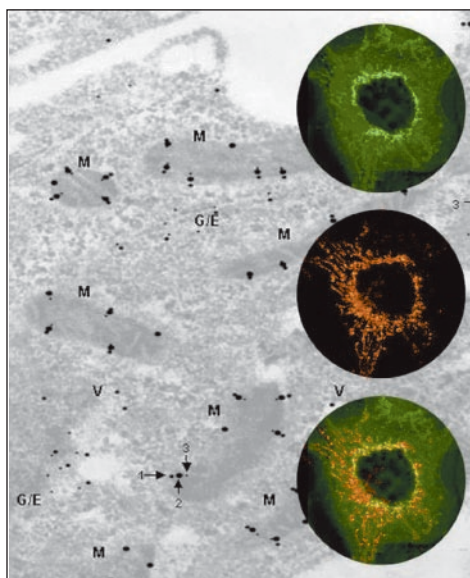
"We found that when APP leaves the nucleus, it can be directed both to mitochondria and to the endoplasmic reticulum," said Avadhani, Harriet Ellison Woodward Professor of Biochemistry and chair of the Department of Animal Biology in the School. "APP has an acidic, negatively charged region that causes it to jam irreversibly while traversing protein transport channels in the mitochondrial membrane. This hampers, and eventually completely blocks, mitochondria's ability to import other proteins and produce cellular energy."

As if suffocating the cell's power plant weren't enough, jammed APP proteins also damaged the mouse neurons studied by Avadhani and co-author **Dr. Hindupur K. Anandatheerthavarada** in a second way. The end of the protein left dangling outside the mitochondrion contains a toxic product called A-Beta. The researchers found that this toxin, a known component of the brain plaques and tangles that are a hallmark of Alzheimer's, is cleaved from the rest of the immobilized protein and accumulates in the cell.

"Researchers have observed many biochemical and biophysical phenomena associated with Alzheimer's disease," said Anandatheerthavarada, research assistant professor of biochemistry and the paper's first author, "but it has remained unclear whether these are causes of Alzheimer's or merely side effects. The pathway we observed, which leads directly to common symptoms, is the first with a demonstrated ability to cause the neuronal death associated with Alzheimer's

disease."

The results are consistent with the progressive nature of Alzheimer's and other neurodegenerative diseases, the scientists said. As pores in the mitochondrial membrane clog with proteins – inaccessible to enzymes that might normally degrade them – cellular function is steadily and inevitably reduced until cell death,



Mitochondria showing the translocation-arrested APP proteins. Circular images show confocal immunofluorescent images of mitochondria.

reached when APP succeeds in suffocating all the cell's mitochondria.

Avadhani and Anandatheerthavarada's results put a dent in cell biology dogma, which

holds that each of the proteins produced in the nucleus can be directed to only one location in the cell. In APP's case, the Penn scientists have shown the targeting sequence within the protein's N-terminal directs it to at least two locations, the mitochondrion and endoplasmic reticulum.

The implication of mitochondrial failure is unexpected because most Alzheimer's researchers, believing the mitochondrion was not on APP's itinerary, have focused on the protein's effects on other organelles. In fact, Avadhani and Anandatheerthavarada found that mitochondria appear to be the only organelles whose membranes have trouble handling APP.

It remains unclear whether APP gets stuck in mitochondria's protein entryways because of its negative charge or bulkiness attributable to improper protein folding. Avadhani and Anandatheerthavarada plan to study the question, which could eventually yield medications to correct the problem.

"A mutant version of APP without the region that's prone to jamming passes into the mitochondria without a hitch," Avadhani said. "This suggests that pharmaceuticals could be developed to fix this domain, either by neutralizing its charge or folding it more tightly."

Avadhani and Anandatheerthavarada were joined in this research by **Dr. Gopa Biswas** and **Mary-Anne Robin**, both of the School's Department of Animal Biology. Their work was funded by the National Institutes of Health.

Construction of State-of-the-art Operating Room at New Bolton Center

New Bolton Center's unique orthopedic surgical facility with its pool recovery system is undergoing a \$2 million renovation and expansion. A new, state-of-the-art operating room for large animals will be constructed in the C. Mahlon Kline Orthopedic and Rehabilitation Center adjacent to the current operating room. That will be refurbished and will be used for minor surgeries and bandage changes. An additional recovery stall will be built adjacent to the recovery pool used for horses emerging from anes-

thesia. The pool will be altered slightly by the removal of the ramp.

While the Kline Center renovations are under way, equine orthopedic surgeries will be handled in an operating suite in another building. Patients will be recovered from anesthesia in a stall.

It is anticipated that the renovation and expansion of the orthopedic surgical facilities will be completed by the end of the summer of 2003.