

Abeta Fragments May Thwart AD Treatment

VITALS

Major Finding: Non-plaque forming fragments of the amyloid beta protein, once thought to be non-neurotoxic, may be more dangerous to the brain than the full-length, plaque-forming amyloid.

Data Source: A series of in vitro studies.

Disclosures: The work was funded by the National Institute of Aging, National Cancer Institute and Alzheimer's Association. None of the authors declared a potential financial conflict.

BY MICHELE G. SULLIVAN

Small fragments of the beta amyloid peptide, previously thought to be nontoxic to the brain, may actually be part of the root cause of Alzheimer's disease, new research findings suggest.

These small beta amyloid (Abeta) fragments group together to create pores that let toxic calcium enter neurons, causing neurodegeneration and cell death, Ramesh Lal, Ph.D., and his colleagues reported in the Proceedings of the National Academy of Sciences of the United States of America (Proc. Natl. Acad. Sci. U.S.A. 2010 [doi/10.1073/pnas.0914251107]).

The findings may offer some insight into the limitations of Alzheimer's drugs targeted to reduce the full-length beta amyloid peptides, Abeta_{1-40/42}, which form the brain plaques seen in Alzheimer's and are the supposed cause of the disease.

While these drugs do decrease the amount of Abeta_{1-40/42}, they also in-

crease the amount of the shorter peptides, which may negate any benefit of the drugs and compound the natural progression of Alzheimer's disease, Dr. Lal said in an interview.

"Any positive effect of these drugs may be masked by the negative effect," of increasing the number of the pore-forming shorter Abeta peptides, said Dr. Lal, professor of Bioengineering and Mechanical Engineering at the University of California, San Diego.

The findings by Dr. Lal and his colleagues, Ruth Nussinov, Ph.D., and Dr. Bruce Kagan, could revolutionize Alzheimer's drug research, said Dr. Richard J. Caselli, professor of neurology at the Mayo Clinic Arizona, Scottsdale. The idea that nonamyloidogenic fragments are themselves neurotoxic preserves a central role for amyloid in Alzheimer's pathophysiology but alters the specifics in ways that could impact future therapeutic development efforts, he said in an interview.

"The amyloid hypothesis has never accounted for the failure of amyloid-clearing immunotherapy to retard the progression of dementia, or for any of the other treatment failures based on the Abeta_{1-40/42} model. This may be a reason why. It is potentially so important in my opinion, that it warrants replication as soon as possible in other labs, and if replicated, should serve as a paradigm-

modifying piece of work in our understanding of amyloid's role in Alzheimer's pathogenesis."

Dr. Lal and his colleagues examined the effect of two short fragments of the Abeta peptide: Abeta₉₋₄₂ and Abeta₁₇₋₄₂.



Neurodegeneration may be the result of the smaller Abeta pieces of the larger plaque-forming peptides.

DR. LAL

They found that both fragments can form mobile ion channels on neuronal cell membranes. When the fragments were added to a culture of mouse fibroblasts that were bathed in a calcium solution, the cells readily took up the calcium. Adding zinc to the mixture, however, blocked the influx of calcium, showing that the pore channel can be inactivated.

When the same procedure was performed on human cortical neurons, the investigators observed an association between the dose of Abeta peptide fragments and how long it took for neurodegeneration to become apparent. The fragments formed pores that allowed calcium to enter the cell. At the smallest dose of the two fragments, it took 24 hours for neurodegeneration to become apparent. It was only detectable with atomic force microscopy. At higher doses, the neu-

rodegeneration was visible with light microscopy by 24 hours. At the highest dose, there was a dramatic reduction in neuronal processes within 15 minutes. Cells showed disrupted, leaking membranes and a decreased number of neurites. Again, cells pretreated with zinc seemed to be protected from damage, even at the highest dosage of the fragments.

The model refines the amyloid hypothesis, Dr. Lal said, suggesting that neurodegeneration may be the result of the smaller Abeta fragments of the larger plaque-forming peptides. "You can put those smaller proteins right on top of neurons in culture and replicate all the damages induced by the full-length amyloid proteins," he said.

"What we are showing is that the smallest nonamyloid-forming peptides might actually be the most important part of the Abeta hypothesis."

The next research step, he said, will be to identify which of the 10-12 amino acids that comprise each ion pore control its behavior. "What we are doing is to try and change each one of the proteins to see how it affects the behavior of the pore," he said. "If you can find the one that closes the pore that would be a target for a small molecule drug."

Because the research was performed completely in vitro, it's too soon to know how—or even whether—the ion pores would affect Alzheimer's disease progression, said Mark A. Smith, Ph.D., an Alzheimer's disease researcher at Case Western University, Cleveland. ■

Sexual Aggression May Be Common in Nursing Homes

BY DAMIAN McNAMARA

FROM THE ANNUAL MEETING OF THE AMERICAN GERIATRICS SOCIETY

ORLANDO — Sexually aggressive behavior might be common between nursing home residents, according to a focus group study.

Most sexual aggression against older adults occurs in long-term care facilities rather than in community settings, according to previous case series. "Very little direct research exists [regarding] what we've begun to call RRSA or resident-to-resident sexual aggression," said Tony Rosen, who conducted the research within the division of geriatrics and gerontology of Cornell University, New York.

Fellow residents are the most common perpetrators of sexually aggressive behavior, not nursing home staff, as sometimes reported in the media, Mr. Rosen said at the annual meeting of the American Geriatrics Society.

Among 103 participants in 16 focus groups including nursing

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Major Finding: Among 16 focus groups made up of 103 residents and staff, 18% of the groups and 38% of participants reported witnessing sexually aggressive behavior in a nursing home setting.

Data Source: Analysis of focus group answers to questions at single, large, not-for-profit skilled nursing facility.

Disclosures: Tony Rosen, a medical student and researcher, had no relevant disclosures.

home employees and some residents, 38% of participants in 18% of the focus groups reported having witnessed sexually aggressive behavior.

Inappropriate touching was the most commonly reported behavior in the study, mentioned in 38% of focus groups by 7% of participants. Residents attempting to get into the bed of another (13% of groups and 18% of participants) and verbal sexual abuse (13% of groups and 5% of participants) were the next most frequent incidents reported.

A behavior cited in the focus groups that surprised the researchers was inappropriate

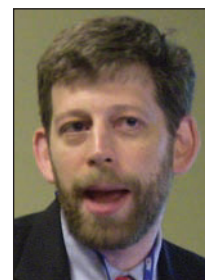
caregiving, mentioned in 6% of groups and by 3% of participants. "Inappropriate caregiving is residents trying to give intimate nursing care to other residents, a phenomenon we did not expect," Mr. Rosen said.

The focus groups included 7 cognitively intact residents and 96 clinical and nonclinical employees from all three shifts at a single, large, not-for-profit long-term care facility. The descriptions of witnessed sexually aggressive behavior came from a larger focus group study evaluating overall resident-to-resident verbal and physical aggression.

"Prevention and management [of these behaviors] are more challenging due to legitimate and increasingly recognized need for sexual expression by nursing home residents," said

Mr. Rosen, a medical student at Cornell.

Mr. Rosen and his colleagues defined RRSA as "negative sexual interactions between long-term care residents, that in a community setting would likely be construed as unwelcome and have high potential to cause physical or psychological distress in the recipient." Consequences for residents include



Management of these behaviors is complicated because residents have a need for sexual expression.

MR. ROSEN

sexually transmitted diseases, agitation, and posttraumatic stress disorder, he said.

Focus group facilitators used semistructured, open-ended interview questions. Average focus group time was 45 minutes.

The researchers also elicited reasons or triggers for RRSA. For example, a resident mistak-

ing another for his or her spouse was reported by 13% of groups and 8% of participants. Cognitive impairment and wandering each were cited as reasons in 13% of groups and by 5% of participants.

"This is a very challenging issue," Mr. Rosen said. "And sexual aggression can be a very charged topic." He recommended that these behaviors be studied and understood in the context of brain disease and agitation-related behaviors.

Resident rooms were the setting for the sexually aggressive behavior mentioned by 13% of groups and 2% of participants. Similarly, nursing home dining rooms were mentioned by 13% of groups and 1% of participants. Somewhat surprisingly, Mr. Rosen said, 6% of groups and 3% of participants also said they saw sexual aggression in main lounges or television viewing areas.

Mr. Rosen made no relevant financial disclosures. ■