Bigger molecular-sized anesthetics do not promote amyloid beta peptide micro-aggregation

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Alzheimer's disease (AD) is a neurodegenerative disorder affecting millions of people worldwide and has become a major global concern. Uncontrolled oligomerization (aggregation) of Aβ peptide is the hallmark of AD and it is believed to be causally related to AD pathomechanism. Intensive research (biophysical, animal model and clinical) is underway to investigate the cause of this unexplained aggregation of Aβ peptide, which is probably triggered by some agent or process in predisposed individuals, and subsequently to trace the molecular pathways involved in the phenomenon.

In the April issue (Vol 20, 1, pages 127-134, 2010) of the *Journal of* Alzheimer's Disease, a laboratory observation based on state-of-the-art nuclear magnetic resonance spectroscopy, suggests a molecular pathway for a possible link between anesthesia and Aβ peptide aggregation. It was observed that the larger sized intravenous anesthetic diazepam (both at clinical and at very high concentration), when incubated in isolation with amyloid beta-peptide, does not promote aggregation in laboratory results monitored serially, even sixty-three days after the onset of incubation. However, if diazepam is co-incubated with halothane (a general inhaled anesthetic with small molecular size, and often used as an add-on in the clinical setting), profound amyloid beta-peptide oligomerization is observed, and the presence of the larger molecular-sized diazepam is rendered ineffective in preventing Aβ oligomerization.

These conclusions have been reached by a team of researchers led by Dr. Pravat K. Mandal, National Brain Research Centre, India, along with collaborators Virgil Simplaceanu, Carnegie Mellon University, USA, and Vincenzo Fodale, from the University of Messina, Italy.

Dr. Mandal's continued and systematic biophysical study on several anesthetics using NMR spectroscopic technique has led to the conclusion that larger sized anesthetics are unable to access the helix-loop-helix region of Aβ peptide containing three specific amino acid residues (G29, A30 and I31); hence, no Aβ oligomerization is initiated. Instead, the region is accessible to small molecular sized anesthetics that initiate the oligomerization process. The "size factor" of these anesthetics and their profound role in Aβ oligomerization is a novel and thought-provoking concept.

Recent literature from the *Journal of the American Medical Association* (*JAMA*, Vol 25, 1760, 2007) has indicated that "some commonly used inhaled anesthetics may cause brain damage that accelerates the onset of Alzheimer disease."

Animal model study on transgenic mice (Journal of Alzheimer Disease, March 2010) has reported "'deleterious impact of isoflurane on behavior, survival, neuronal cell death, and processing of proteins involved in neurodegeneration is restricted to subjects with special susceptibility but does not affect normal subjects."

Dr. Mandal and his colleagues strongly believe that "at this juncture, results from our biophysical 'in-vitro' studies cannot be translated directly to apply in the clinical setting but it certainly promotes further investigation at the clinical level. This area of research is potentially important for aged population and person at risk for AD."

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