

Oxidative Damage Occurs Before Alzheimer's Plaques

Research into the causes of Alzheimer's Disease shows that amyloid plaques develop while the illness is taking over the brain but is still not clinically evident.

Accordingly, the most common scientific belief holds that those plaques contribute to or cause the oxidative damage and inflammation that occur and, ultimately, destroy brain cells.

Now, a new study at the University of Pennsylvania School of Medicine has demonstrated that oxidative damage precedes the plaques -- a reversal of existing theory that opens new paths of inquiry in combating an illness that afflicts one out of every 10 persons over the age of 65.

"Alzheimer's Disease is a very complex disease that does not appear to have a single cause, but our research indicates that oxidative stress is probably a primary event in the course of the illness," said Domenico Pratico, MD, of the Department of Pharmacology in Penn's School of Medicine and a member of Penn's Center for Experimental Therapeutics. He is corresponding author of the study, which is published in the June 15 issue of *The Journal of Neuroscience*.

The primary target of Alzheimer's Disease (AD) is the hippocampus, followed by the frontal and temporal lobes of the brain, all of which can lose between 30 and 40 percent of their neurons as the disease progresses.

Most scientists investigating the illness base their work on one of two main theories:

The first holds that as amyloid plaques develop, they cause an inflammation in microglia cells that backfires, stimulating the production of cytokines that attack and damage neurons.

The second theory is based on the action of free radicals. About 95 percent of the brain is made up of fatty lipids that, when attacked by free radicals, undergo peroxidation (oxidative damage.) That leads, in turn, to cell malfunction and eventual cell death.

It is known that amyloid beta protein can produce free radicals on its own, as well as stimulate other cells to do the same. Many scientists believe that a build-up of amyloid plaques causes a parallel increase in free radicals, which eventually reach the point where they overwhelm the brain's power to destroy them -- resulting in what is called oxidative stress.

At the core of both theories is the belief that amyloid plaques constitute an initiating factor in the onset of Alzheimer's Disease. Pratico and his colleagues decided to establish whether that is true.

They discovered that free radicals show up on the scene even earlier.

"This opens a lot of interesting hypotheses for therapeutics," Pratico said. "If you reduce oxidative stress very early, when they are very young, can you prevent the formation of amyloid? And by how much?"

Others who collaborated in the study were Kunihiro Uryu, PhD, John Q. Trojanowski, MD, PhD, and Virginia M.-Y Lee, PhD, of Penn's Department of Pathology and Laboratory Medicine. Trojanowski and Lee are codirectors of the Center for Neurodegenerative Disease Research and Uryu is a member of the center's staff.

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By Ellen O'Brien