Study suggests a second dimension to Alzheimer's disease

September 7 2006

The genes responsible for an inherited form of Alzheimer's disease play a direct role within cells that has largely been overlooked, according to a report in the September 8, 2006 issue of the journal *Cell*, published by Cell Press. The findings suggest that there may be an additional dimension to the irreversible neurodegenerative disorder, which potentially suggests a new avenue for the pursuit of therapies, the researchers said.

The researchers found that two genes mutated in familial Alzheimer's disease known as presenilins may control the balance of calcium within cells by acting as a calcium channel. Calcium is an important signaling molecule, with effects on the nervous system that include functions relevant to learning and memory, the researchers said. The research team also discovered that the mutant forms of presenilin--which have been linked to about 40 percent of familial Alzheimer's disease cases--lose the ability to serve this function.

Presenilins are primarily known for their role as an enzyme that cleaves amyloid precursor protein (APP) to form amyloid ß-peptide, the principal constituent of the plaques that riddle the brains of Alzheimer's patients.

"Clearly it makes sense that presenilin's role in cleaving APP would affect Alzheimer's disease," said Ilya Bezprozvanny of UT Southwestern Medical Center at Dallas. "But our findings suggest a totally different angle, raising the possibility that presenilin's effect on the disease may be

two-fold."

Bezprozvanny cautioned, however, that further work is required to determine whether or not the genes' other role in calcium regulation has a causal connection to the symptoms of Alzheimer's disease.

Alzheimer's disease affects nearly 2% of the population in industrialized countries. Most cases of the disease are of unexplained origin and are characterized by late onset in people over the age of 60. A small fraction of cases are characterized by an earlier onset and genetic inheritance.

The two forms of the disease otherwise share many common characteristics, Bezprozvanny said, and it is generally assumed that study of familial Alzheimer's can lead to new insights into general mechanisms underlying the disease.

Earlier studies had linked mutations in the presenilin gene to abnormal calcium signaling and suggested that calcium might have some relevance to Alzhiemer's disease. However, the mechanistic basis for presenilin's apparent effects on calcium remained unclear, leaving a question as to whether the proteins played a direct role.

The researchers now report from studies in mice that presenilins can form ion channels. The effects of presenilin could account for about 80% of the calcium leaked from a membrane bound cellular compartment called the endoplasmic reticulum, they found.

Cells with the mutant presenilin become "overloaded" with calcium, Bezprozvanny explained, which heightens the strength of the calcium signal. Moreover, the heightened calcium signal was reversed in mutant cells in which the scientists restored normal presenilin. They further showed presenilin's role in calcium signaling to be independent of its role in the production of amyloid ß.

The findings suggest that drugs that restore normal calcium levels might be useful for treating Alzheimer's disease, Bezprozvanny said. Indeed, he added, a drug called memantine, which is already in use against Alzheimer's, acts on receptors that are a component of the calcium pathway.

The development of Alzheimer's drugs has almost exclusively focused on amyloid plaques, he said. The current findings begin to suggest the possibility that a combination therapy targeting both amyloid and calcium signaling might be a "best case scenario," Bezprozvanny speculated.

Aberrant calcium signaling might also be a common link among multiple neurodegenerative diseases, he added. For example, he noted that his group earlier found evidence for a direct effect of abnormal calcium signaling in Huntington's disease.

Source: Cell Press