Mechanisms that prevent Alzheimer's Disease: Enzymatic activity plays key role

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In a project involving the collaboration of several institutes, research scientists of the Johannes Gutenberg University Mainz have succeeded in gaining further insight in the functioning of endogenous mechanisms that protect against the development of Alzheimer's disease. It was found that the activity of the enzyme α-secretase is mainly responsible for the protective effect.

"In the past, we postulated that the enzyme α-secretase was involved in preventing the formation of cerebral plaques characteristic of Alzheimer's disease and also enhanced cerebral functions, such as learning and memory," explained Professor Falk Fahrenholz of the Institute of Biochemistry. His research group has been working in cooperation with the Clinic of Psychiatry and Psychotherapy of the university's Faculty of Medicine and the Central Animal Laboratory Facility (ZVTE) to discover the mechanism for the beneficial effects of α-secretase. The *Journal of Alzheimer's Disease* (JAD) presents the results of this project in its February 2009 issue.

α-secretase is an endogenous enzyme that is present in the nerve cells of the brain, where it is responsible for the cleavage of an Aβ into Aβ domain. The result is a soluble protein fragment that promotes the growth of nerve cells and thus prevents the development of cerebral deterioration caused by Aβ. However, if the enzyme β-secretase is active, a chain reaction is initiated that subsequently results in the development Aβ initializing the cascade of Alzheimer's disease through formation of Aβ. "You could say that α-secretase is the good enzyme,

and β-secretase the bad en-zyme," Fahrenholz commented. "We now want to find out how to activate this 'good' enzyme or increase its concentrations in the brain as a way of combating this disease."

With this in view, the collaborating partners have been investigating whether the positive effects of α-secretase are attributable to its enzymatic activity or whether the protective effect is due to other properties of the enzyme. Enzymes play an important role in the metabolism as they control, regulate and catalyse numerous biochemical processes. "The α-secretase enzyme is a highly complex one, with many other functions. For example, it also relays signals from the intercellular space into cells and interacts with molecules on other cells." Fahrenholz and his colleagues have now established, following investigations in a transgenic mouse model, that it is the enzymatic activity alone that guarantees the protective effects. If this activity is neutralised, the laboratory mice exhibit the symptoms that are characteristic of Alzheimer's disease: impaired learning ability, poor memory capacity and the build-up of Aβ plaques. It is thus possible that the enzymatic activity of α-secretase could represent the starting point for the development of future treatments.

At the same time, the researchers were able to confirm with their experiments that it is not the plaque build-up itself that is responsible for the loss of memory capacity. The cytotoxic substances that accumulate in plaques only destroy neuron synapses when they are still in solution. Prof. Fahrenholz concludes: "It is important to consider other aspects in addition to the plaques themselves, particularly their precursors, which are a real cause of the disease."

More information: Anja Schroeder, Falk Fahrenholz, Ulrich Schmitt, Effect of a dominant-negative form of ADAM10 in a mouse model of Alzheimer's Disease, *Journal of Alzheimer's Disease*, February 2009, Volume 16:02

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