New findings contradict dominant theory in Alzheimer's disease

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For decades the amyloid hypothesis has dominated the research field in Alzheimer's disease. The theory describes how an increase in secreted beta-amyloid peptides leads to the formation of plaques, toxic clusters of damaged proteins between cells, which eventually result in neurodegeneration. Scientists at Lund University, Sweden, have now presented a study that turns this premise on its head.

The research group's data offers an opposite hypothesis, suggesting that it is in fact the neurons' inability to secrete beta-amyloid that is at the heart of pathogenesis in Alzheimer's disease.

The study, published in the October issue of the Journal of Neuroscience, shows an increase in unwanted intracellular beta-amyloid occurring early on in Alzheimer's disease. The accumulation of beta-amyloid inside the neuron is here shown to be caused by the loss of normal function to secrete beta-amyloid.

Contrary to the dominant theory, where aggregated extracellular beta-amyloid is considered the main culprit, the study instead demonstrates that reduced secretion of beta-amyloid signals the beginning of the disease.

The damage to the neuron, created by the aggregated toxic beta-amyloid inside the cell, is believed to be a prior step to the formation of plaques, the long-time hallmark biomarker of the disease.

Professor Gunnar Gouras, the senior researcher of the study, hopes that the surprising new findings can help push the research field in a new direction.

"The many investigators and pharmaceutical companies screening for compounds that reduce secreted beta-amyloid have it the wrong way around. The problem is rather the opposite, that it is not getting secreted. To find the root of the disease, we now need to focus on this critical intracellular pool of beta-amyloid.

"We are showing here that the increase of intracellular beta-amyloid is one of the earliest events occurring in Alzheimer's disease, before the formation of plaques. Our experiments clearly show a decreased secretion of beta-amyloid in our primary neuron disease model. This is probably because the cell's metabolism and secretion pathways are disrupted in some way, leading beta-amyloid to be accumulated inside the cell instead of being secreted naturally", says Davide Tampellini, first author of the study.

The theory of early accumulation of beta-amyloid inside the cell offers an alternate explanation for the formation of plaques. When excess amounts of beta-amyloid start to build up inside the cell, it is also stored in synapses.

When the synapses can no longer hold the increasing amounts of the toxic peptide the membrane breaks, releasing the waste into the extracellular space. The toxins released now create the seed for other amyloids to gather and start forming the plaques.

More information: "Impaired ?-Amyloid Secretion in Alzheimer's Disease Pathogenesis" www.jneurosci.org/content/31/43/15384.full

Provided by Lund University