A new strategy required in the search for Alzheimer's drugs?

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In the search for medication against Alzheimer's disease, scientists have focused – among other factors – on drugs that can break down Amyloid beta (A-beta). After all, it is the accumulation of A-beta that causes the known plaques in the brains of Alzheimer's patients. Starting point for the formation of A-beta is APP. Alessia Soldano and Bassem Hassan (VIB/KU Leuven) were the first to unravel the function of APPL – the fruit-fly version of APP – in the brain of healthy fruit flies.

Alessia Soldano (VIB/KU Leuven): "We have discovered that APPL ensures that brain cells form a good network. We now have to ask ourselves the question whether this function of APPL is also relevant to Alzheimer's disease."

Bassem Hassan (VIB/KU Leuven): "Since we show that APP and APPL show similar activities in cultured cells, we suspect that APP in the human brain functions in the same manner as APPL in the brain of fruit flies. Hopefully we can use this to ask and eventually answer the question whether A-beta or APP itself is the better target for new drugs."

Plaques in the brain: Cause or effect

The brain of a person with Alzheimer's disease is very recognizable due to the so-called plaques. A plaque is an accumulation of proteins that are primarily made up of Amyloid beta (A-beta), a small structure that splits off from the Amyloid Precursor Protein (APP). We have been dreaming

for a long time of a drug that can break down A-beta, but we should be asking ourselves whether this is really the best strategy. After all, it is not yet clear whether the plaques are a cause or effect of Alzheimer's disease. In order to answer this question, it is important to determine the function of APP in healthy brains.

Optimum communication between brain cells

Alessia Soldano and Bassem Hassan study APPL, the fruit-fly version of APP. APPL is found throughout the fruit-fly brain, but primarily in the so-called alpha-beta neurons that are vital to learning processes and memory. The alpha-beta neurons must form functional axons for optimum functioning. Axons are tendrils projecting from the neuron, which are essential for communication between neurons. The VIB scientists had previously shown that APPL is important for memory in flies. Now, they have discovered that – in the developing brain of a fruit fly – APPL ensures that the axons are long enough and grow in the correct direction. APPL is therefore essential in the formation of a good network of neurons. The question is whether or not it is a good strategy to target a protein with such an important function in the brain in order to combat Alzheimer's disease.

More information: Soldano, et al. An Axonal Growth Pathway Requires an Alzheimer's Protein, *PLOS Biology* 2013. www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1001559

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