Alzheimer's Disease -giving synaptic vesicles a second glance

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Alzheimer's Disease (AD) is the most common form of dementia with more than 35 million people affected world-wide. It is most commonly seen in those over 60 but sometimes even in those that are younger. We do not yet have a cure for the disease and those who suffer from it slowly and irreversibly lose their memory and thinking skills. A lot of research is dedicated to trying to understand what causes it, so that eventually a cure can be found. At this stage we have several hypothesis regarding to how the disease develops, one of them is called the 'Amyloid hypothesis'. According to it a protein fragment, called amyloid-beta (Abeta), starts accumulating in the brains of some people. Somewhere inside the brain cells is a protein called APP that is cut by an enzyme called Gamma-secretase to produce Abeta. Once Abeta is made the brain cells release it into the brain fluid. Gradually the concentration of Abeta in the brain gets so high that it becomes toxic for the brain cells, killing them. As the brain cells die, memory and thinking starts getting affected and slowly dementia develops.

In the 1990s researchers were looking at different parts of the brain cell trying to identify where exactly APP is located, so that they could stop it from being cut into Abeta. They suspected that it could be in the synaptic vesicles. Synaptic vesicles are tiny balloon-like structures inside the brain cells, they contain different chemicals, molecules and proteins. When our brain cells want to communicate with each other they do it by popping these balloons and empting their contents out of the cell and into the brain. From what the researchers saw, it seemed like APP was not there. Recently however, two research groups looked at the synaptic vesicles again and found that APP does seem to be there. One of the groups also found that the enzyme that cuts APP into Abeta is possibly also there. However, the synaptic vesicles that they studied were not extremely clean which could mean that what they saw could also be contamination from other parts of the brain cell.

Now the researchers want to develop a method to see whether Abeta is released when the brain cells pop the synaptic vesicles, and I too have worked on it. To check the Abeta release I needed to first isolate the cells from the brain in a way that they would still behave as they do in a living brain. I was unable to develop such a method, but knowledge was gained and the work was progressive.

Next in my experiments, I investigated whether the enzyme that cuts APP is present in purified synaptic vesicles, and if so, check whether Abeta is produced there. What I found indicates that the enzyme is present in the synaptic vesicles, and also Abeta is produced there.

One possible way to treat AD would be to stop Abeta production by making drugs that prevent Gamma-secretase from cutting APP. However, when previously such drugs were given to AD patients such severe side-effects were seen that the treatment had to be discontinued. It is believed that the side-effects occurred because when Gamma-secretase is prevented from cutting APP is also becomes unable to cut another protein called Notch. Sometimes the same proteins and enzymes can be found in different parts of the cell having different functions. My experiments indicate that the Notch protein is not cut by the enzyme Gamma-secretase in the synaptic vesicles. So it could be possible to make drugs that specifically target the synaptic vesicles and there prevent Gamma-secretase from cutting APP. This could stop Abeta production in the brains of AD patients without provoking any Notch-related side-effects.

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