Solving the Riddle of Amyloid and Alzheimer's Disease

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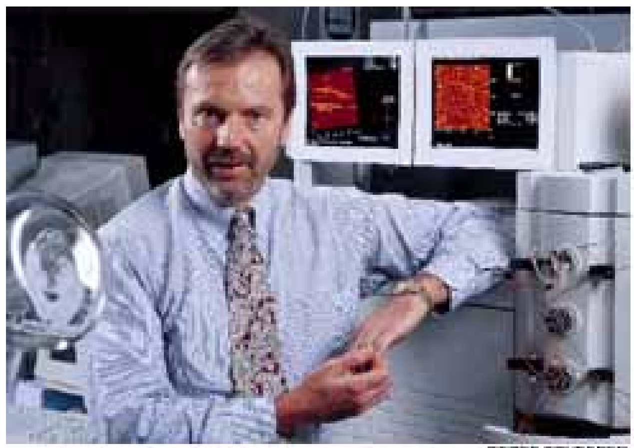
....Alzheimer's research today moves at a very rapid pace. Not a single month goes by without some major Alzheimer's story. Each brief news spot on CNN raises our hopes that one day soon, Alzheimer's disease will be treatable or even preventable. But when the publicity dies down, we are left waiting and hoping for that next big breakthrough, the one that we hope will translate much more quickly into meaningful treatment.

....Earlier this year, we published a paper that might eventually prove to be just this type of meaningful discovery. The paper describes new, potent neurotoxins called amyloid ß-derived diffusible ligands (ADDLs), and provides details about the biochemical malfunctions they activate. Our findings stimulate a new way of thinking about the cause and progression of Alzheimer's disease. We believe that it may actually be possible to block and even reverse the early symptoms of Alzheimer's disease, because these early symptoms, and also subsequent disease progression, may stem from ADDL-triggered malfunctions in nerve cells.



Dr. Grant Krafft in his laboratory at the ENH Research Institute & Northwestern University

....To put our findings into perspective, a brief overview is helpful. In 1907, an autopsy on a demented patient of a German psychiatrist, Alois Alzheimer, revealed highly unusual brain pathology that Alzheimer called senile plaques and neurofibrillary tangles, and these hallmarks even today define the disease. For many years they also have served as the framework for most Alzheimer's research. Unfortunately, these hallmarks really couldn't tell us what causes Alzheimer's disease, anymore than ashes or glass fragments could tell a fire inspector what started the house fire.

....The first genuinely useful clues came in the 1980's. The major plaque protein known as amyloid ß (Aß) was identified in 1984, and in 1987 the gene for its precursor protein (APP) was discovered. Scientists then found mutations in this gene that caused certain early-onset familial Alzheimer's disease (FAD), and over time, it was shown that these mutations caused increased levels of Aß. Mutations in two new FAD genes, known as presenilins I & II, were found just a few years ago, and remarkably, these mutations also increased Aß-levels. So taken together, these FAD mutations now provide compelling evidence that *elevated* Aß does cause Alzheimer's disease, but they do not tell us *how*.

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….Many scientists surmised that Aß found within plaques was responsible for killing nerve cells. In laboratory studies, Aß could be toxic to nerve cells, but these results were difficult to reproduce. Moreover, many neuropathologists doubted the toxicity of Aß because brain tissue often shows plaques with no dead neurons nearby, or dead neurons with no plaques nearby. And sometimes, brain tissue from normal individuals shows large deposits of Aß, but no trace of dead or dying neurons, or any type of symptoms.

….Our early Aß toxicity experiments also had generated inconsistent results, but there was one fortunate difference. Working with Caleb E. Finch, PhD, we discovered that mixing Aß with an inflammatory brain protein known as apo J made the Aß much more toxic, and it actually *decreased* the amount of Aß *fibrils* in the mixture. This was quite surprising since most scientists have thought that the toxicity was linked to the fibril form of Aß. Instead of fibrils, we identified tiny ball-like structures about two million times smaller than a centimeter in these mixtures, using a high resolution imaging technique called "atomic force microscopy". Apparently, apo J causes the formation of these toxic globular structures (ADDLs) rather than the preferred insoluble fibrils found in plaques. This may explain why anti-inflammatory drugs are effective in lowering Alzheimer's disease risk.

….Our studies of ADDLs and nerve cells showed that ADDLs are very potent and rapidly trigger biochemical responses, some of which eventually lead to nerve cell death. Certain responses suggest that ADDLs might be interfering directly with a key process involved in learning and memory called "long term potentiation" (LTP). We tested ADDLs in model systems involving direct injection into brains of mice or addition to cultured brain slices, and indeed, ADDLs blocked LTP. In other words, ADDLs severely impaired information storage capability, and at a time well before any nerve cells died. So it seems that early impairment in Alzheimer's disease might be caused when ADDLs trigger malfunctions in nerve cells that otherwise are still healthy.

….If this scenario is correct, it may be possible for a suitable ADDL-blocking drug to rescue nerve cells from the effects of ADDLs, and even reverse learning and memory impairment in nerve cells that have not died or suffered irreversible biochemical damage.

….With these exciting possibilities on the horizon, several points must be emphasized. First, our studies have been carried out in model systems, so the relevance to Alzheimer's disease can only be inferred from similarities between processes evident in Alzheimer's brain tissue and those activated by ADDLs. Second, although our results are intriguing, we must remember that no theory is ever proved. Practical validation can emerge only if we translate our findings into ADDL-blocking drugs, and demonstrate them to be effective in stopping and reversing early impairment in Alzheimer's disease victims. Until such time, we continue to study cellular and molecular mechanisms of Alzheimer's disease, identify additional drug targets, and implement ADDL drug discovery activities.

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