Features

Chroniques

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Can Med Assoc J 1997;156:1040-2

Amyloid ß protein and Alzheimer disease

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In Brief

AMYLOID ß PROTEIN IS PREDOMINANT IN SENILE PLAQUES, the neuropathologic hallmarks of Alzheimer disease. Researchers in Winnipeg have shown that this protein can overstimulate certain hydrolytic enzymes to break down the phospholipid building blocks of the brain-cell wall. They speculate that the abnormal destruction of phospholipids gradually drains the energy resources a neuron uses to rebuild its membrane. As neurons "burn out," the brain loses its ability to function normally. In view of evidence that NSAID therapy may interfere with the hydrolysis of phospholipids, the researchers will focus on finding an NSAID-related compound effective against Alzheimer disease.

En bref

LA PROTÉINE AMYLOÏDE ß EST PRÉDOMINANTE DANS LES PLAQUES SÉNILES, indication neuropathologique de la maladie d'Alzheimer. Des chercheurs de Winnipeg ont démontré que cette protéine peut surstimuler certaines enzymes hydrolytiques qui dissocient les phospholipidies, éléments fondamentaux de la paroi des cellules du cerveau. Ils pensent que la destruction anormale des phospholipides épuise graduellement les ressources énergétiques qu'un neurone utilise pour reconstituer sa membrane. À mesure que les neurones «brûlent», le cerveau perd sa capacité de fonctionner normalement. Compte tenu des données probantes selon lesquelles une thérapie aux AINS peut nuire à l'hydrolyse des phospholipides, les chercheurs essaieront avant tout de trouver un composé lié aux AINS qui est efficace contre la maladie d'Alzheimer.

Research that links Alzheimer disease to a protein that destroys brain-cell membranes has produced some encouraging results for a group of Winnipeg scientists.

Dr. Julian Kanfer, the neurochemist whose research team has been studying the relation between the disease and amyloid ß protein, is cautiously optimistic about the results. A professor in the Department of Biochemistry and Molecular Biology at the University of Manitoba, Kanfer received a 2-year research grant worth $100 000 from the Alzheimer Society of Manitoba.

"To my knowledge," says Kanfer, "my lab is the only one in the world that has undertaken a study of amyloid ß protein and the role it plays in the phospholipid destruction of brain neurons. Much research has focused on the relationship between this protein and the role of calcium or free-radical damage to neurons in Alzheimer's patients." Because it is unique and has yielded some encouraging findings, Kanfer's work has attracted the interests of neuroscientists in Japan and other countries.

A vexing problem

The publication in 1995 of Kanfer's results[1] is the product of 10 years' work on a problem that has vexed scientists for decades: What chemical changes occur in the brain to cause the characteristic symptoms of Alzheimer disease?

While he was head of biochemistry at the Eunice Kennedy Center for Mental Retardation in Waltham, Mass., from 1969 to 1975, Kanfer investigated

Daniel Wexler photo

Drs. Julian Kanfer (left) and Indrapal Singh are investigating a link between between Alzheimer disease and the Amyloid ß protein

childhood storage diseases then classified as "inborn errors of metabolism." At that time no one understood what caused these fatal neurologic disorders. In association with Harvard University, the Massachusetts General Hospital and the National Institutes of Health, Kanfer's research team studied the metabolism of compounds that accumulate in children with Gaucher and Niemann–Pick disease. They demonstrated that deficiencies of ß-glucocerebrosidase and sphingomyelinase were responsible for the fatal accumulation of storage compounds in these patients.[2]

Kanfer says storage compounds are naturally occurring substances that do not accumulate in healthy organs because they are degraded by enzymes. Without sufficient enzyme activity in the brain to limit their production, "the compounds run amok, accumulating to the point where they interfere with normal neuronal activity."

Kanfer's group was the first to demonstrate that hydrolytic enzymes such as ß-glucocerebrosidase, sphingomyelinase and phospholipase A, C and D play an important role in maintaining cellular homeostasis in the brain. Their early research set the model for continuing worldwide studies of hydrolytic enzymes in storage diseases.[3]

Today some of Kanfer's own work in this area shows promise in the search for a cure for Alzheimer disease. "We didn't set out to discover a cause or a cure for Alzheimer's," Kanfer says, "but it suddenly occurred to us that our enzyme studies might lead to a greater understanding of the disease."

Senile plaques

His research is focused on amyloid ß protein found predominantly in the senile plaques that are the neuropathologic hallmark of Alzheimer disease. "Although normal aging brains have a few senile plaques, the brains of [people with] Alzheimer's disease exhibit a vastly increased number of these garbage pails of cell debris. Amyloid ß protein is prominent among the debris."

The protein has the ability to overstimulate the hydrolytic enzymes phospholipase A, C and D to break down the phospholipid building blocks of the brain-cell wall.[1]

Kanfer and his colleagues, Dr. Indrapal Singh and technician Douglas McCartney of the University of Manitoba, and Dr. Giuseppe Sorrentino of the University of Napoli, Italy, hypothesize that the accumulation of amyloid ß protein and the abnormal enzyme activity it triggers may cause or contribute to the neuronal degeneration characteristic of Alzheimer disease. Some reflections of this abnormality have been observed both in vivo[4] and in vitro[5] by nuclear magnetic resonance spectroscopy (MRS), which consistently shows an increase in compounds related to phospholipid degeneration.

For example, Kanfer says, in-vitro phosphorous-31 MRS analysis shows elevated phosphomonoester and phosphodiester levels in perchloric acid extracted from brain tissue taken post mortem from people with Alzheimer disease.[5] Correlations with neuropathologic markers such as senile plaques indicate that phosphomonoester levels may increase early in Alzheimer disease, whereas phosphodiester levels appear to increase at a later, degenerative stage. Kanfer also cites 3 in-vivo phosphorous-31 MRS studies[4,6,7] that support the hypothesis that phosphomonoester levels are elevated in the early stage of the disease.

The breakdown of phospholipids has unpleasant consequences for a brain neuron. For example, says Kanfer, lysophospholipid, one of the products of phospholipase A, "is a naturally occurring detergent that dissolves cell walls much like laundry soap dissolves dirt in clothing."

Kanfer's team speculates that the abnormal breakdown of phospholipids "gradually overcomes the limited energy resources a neuron can mobilize to rebuild its membrane as well as perform all the other functions required of it." As a result, the cell finally burns out like a light bulb. As more and more neurons die, the brain begins to lose its ability to work properly, and the disease symptoms appear.

The arthritis connection

Kanfer finds it interesting that patients with rheumatoid arthritis are reported to have a lower incidence of Alzheimer disease than the general population.[8] He feels

that a reasonable explanation is that the treatment of these patients with NSAIDs[9] "may protect by interfering with hydrolysis of phospholipids." His research team has begun to test this hypothesis; early findings are promising.

Kanfer credits Dr. Patrick McGeer and associates, of the Department of Psychiatry at the University of British Columbia with conducting some of the earliest studies on the neuroimmunologic properties of NSAIDs. That research led to an understanding of how NSAIDs lower the incidence of Alzheimer disease among patients with rheumatoid arthritis by controlling "a chronic inflammatory state of the brain in Alzheimer's disease."[10]

"If our clinical model reflects what is going on in the brain, then a designer drug can be made that will intervene in this process, and we will have a therapy to combat Alzheimer's."

The results of the research, which began 8 years ago, were recently confirmed by a federal task force.[11] Kanfer says McGeer's team and researchers in other countries are continuing to investigate this possible approach to the prevention of Alzheimer disease.

Current pharmacologic approaches to treatment have had limited success. "At present," says Kanfer, "tacrine and all the other Alzheimer's drugs are not universally accepted as beneficial." Drugs such as tacrine are intended to counteract the marked decrease in acetylcholine levels typically found in Alzheimer patients by preventing the hydrolysis of acetylcholine, thus increasing the amount available to function as a neurotransmitter. Despite the limited success of this approach, Kanfer says drug companies continue to pour research dollars into the development of acetylcholine esterase inhibitors. In addition, consumers can "still find 'brain-food' preparations on the shelves of health-food stores that are derivatives of choline, a building-block of acetylcholine. These concoctions are sold to people as memory enhancers, but in reality they have little effect on memory, nor do they work as a cure for Alzheimer's disease."

On the horizon

Kanfer hopes that his research may eventually lead to the discovery of a compound that can be developed into an effective agent against Alzheimer disease. He feels his current study of the apparent ability of NSAIDs to interfere with phospholipid hydrolysis is a good starting point. "If our clinical model reflects what is going on in the brain, then a designer drug can be made that will intervene in this process, and we will have a therapy to combat Alzheimer's."

Kanfer admits that much more research is required into all aspects of the disease. For example, there is still no specific test to predict it. "Apolipoprotein E testing is diagnostic," he says, "but it is not predictive." Kanfer and some of his colleagues are currently forming their own group within the University of Manitoba to conduct research, to lobby for increased private and public funding, and to create greater public awareness of the disease.

"Ultimately, a cure for Alzheimer's, or even a method to slow down the course of the disease, will benefit all of us."

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