NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Cellular Prion Protein May Be a Receptor for Oligomeric Amyloid-Beta

Novel approaches to unlocking the mystery of Alzheimer's disease are underway in labs all over the world. In this month's column, we review the surprising discovery that a protein normally equated with Creutzfeldt-Jakob disease may be a receptor for oligomeric amyloid-beta and may mediate the resulting consequences of impaired neuronal long-term potentiation, dendritic spine retraction, and memory loss that characterize Alzheimer's. The discovery may provide yet another therapeutic target for the disease.

BY RICHARD J. CASELLI, M.D.

Cellular prion protein functions as a receptor for the amyloid-beta-42 (Abeta42) oligomers that are known to disrupt the memory-related functions of synaptic junctions between neurons, especially those in the hippocampus in Alzheimer's disease (AD), according to researchers at Yale University, New Haven, Conn.

This novel role of cellular prion protein (PrP^{C}) in mediating the deleterious effects of Abeta42 oligomers was not dependent on the infectious, pathogenic conformation of the protein, PrP^{Sc}, which causes fatal transmissible spongiform encephalopathies such as Creutzfeldt-Jakob disease and mad cow disease, Dr. Juha Laurén and his colleagues reported in Nature (2009;457:1128-32).

In a screen of cells that expressed complementary DNA from adult mouse brain, the researchers found that synthetic oligomers of Abeta42 bound only to proteins that were identified as mouse PrP. Abeta42 bound to cells that expressed PrP^{C} with the same apparent affinity as it did to hippocampal neurons. In more specific screens of other proteins, they detected several other proteins that bound to oligomeric Abeta42, but none of these had the same high affinity and high selectivity for the oligomeric peptide as did PrP. However, in cultures of cells from mice that lacked the PrP gene, the researchers found that the binding of Abeta42 to neurons was reduced by only 50%, suggesting that "PrP^{C} cannot be the only cell-surface molecule binding Abeta42 oligomers."

Abeta42 oligomers did not inhibit long-term potentiation (LTP), the neural correlate of memory formation, in hippocampal slices from mice that lacked the PrP gene. LTP in these mice was indistinguishable from baseline levels in wild-type mice. The lack of LTP sensitivity to Abeta42 oligomers in mice without the PrP gene "indicates that PrP^{C} acts as a receptor for Abeta42 oligomers mediating inhibition of LTP in wild-type slices [or that] chronic loss of PrP^{C} may lead to developmental and/or compensatory effects that account indirectly for Abeta42 oligomer ineffectiveness," wrote Dr. Laurén and his coinvestigators.

In a commentary, Dr. Moustapha Cisse and Dr. Lennart Mucke of the University of California, San Francisco, wrote that "to assess the clinical relevance and therapeutic potential of these findings, interaction between PrP^{C} and Abeta oligomers must be confirmed in patients with Alzheimer's disease, and the relationship between PrP^{C} levels and cognitive decline should be explored. It would also be of interest to determine whether the cognitive deficits and behavioral alterations seen in mouse models of Alzheimer's disease can be prevented by ablating or reducing PrP^{C}" (Nature 2009;457:1090-1).

Dr. Caselli's comment: The unexpected and intriguing link between PrP^{C} and Abeta42 oligomers may eventually lead to another piece of the Alzheimer's disease puzzle. Nobel laureate Dr. Stanley B. Prusiner introduced the world to prions, infectious particles that are now thought to cause all of the spongiform encephalopathies from mad cow disease to Creutzfeldt-Jakob disease. PrP has been shown to be a normal human protein that can exist in one of two conformational states: a normal cellular form PrP^{C} and an abnormally folded infectious form PrP^{Sc} that is responsible for Creutzfeldt-Jakob disease.

But the role of PrP is complex. Dr. Eric R. Kandel, who received the Nobel prize for his work on the physiology of memory, and his colleagues have suggested that PrP might be essential for the maintenance of long-term memory—memories that last longer than the proteins comprising the facilitated synapses that underlie them—and that the conformational change of PrP^{C} into PrP^{Sc} occurs normally (with appropriate regulation) to achieve this (Cell 2003;115:879-91; Cell 2003;115:893-904).

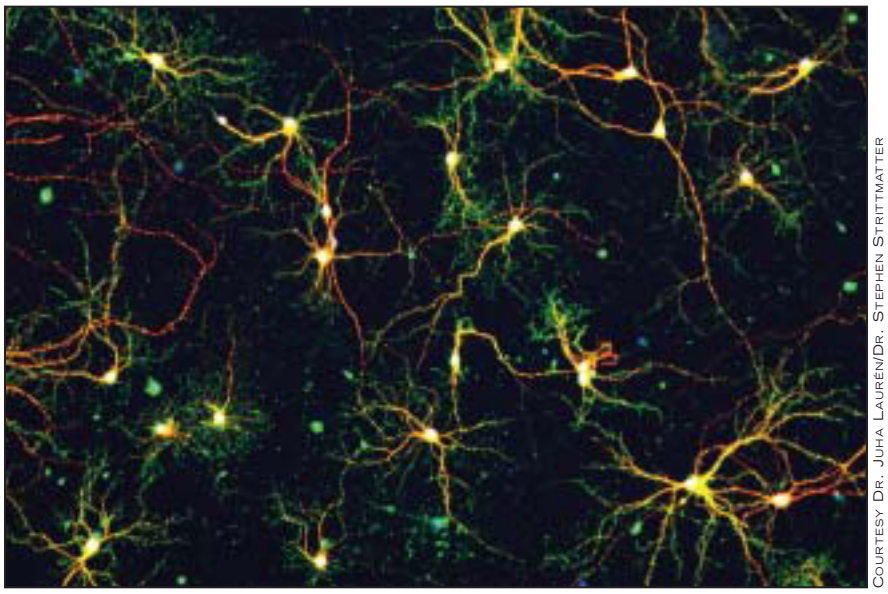
In humans, there is some evidence to suggest that allelic variations of the PrP gene are associated with altered long-term memory function (Hum. Mol. Genet. 2005;14:2241-6), and even predisposition to Alzheimer's disease (Neurology 2004;63:364-6). The more direct demonstration by Dr. Laurén and his colleagues of the potential role that PrP can play in memory and Alzheimer's disease is therefore of great interest. The investigators have shown that it is the seemingly "standby" PrP^{C} conformation, and not the "activated" PrP^{Sc} conformation, that binds Abeta oligomers and that in turn, leads to impaired LTP. The high affinity is striking, so that even though other membrane-bound proteins such as the receptor for advanced glycation end products (RAGE) binds Abeta more weakly, there is the possibility that the binding of PrP^{C} to Abeta oligomers is no mere coincidence.

In addition, as pointed out in the commentary by Dr. Cisse and Dr. Mucke, the fact that alpha-secretase cleaves off amino acids 95-110 of PrP^{C}, which appear to be crucial for binding Abeta oligomers, suggests that the interaction may have real pathophysiologic significance. Demonstration in humans will be essential, and the identification of an Abeta "receptor" implies the potential development of receptor antagonists that might block such binding.

Immunologic therapies (as preliminarily demonstrated by Dr. Laurén and his colleagues) may work through such a role as well by either binding to the 95-110 epitope or to the PrP receptor itself. It would be the ultimate paradox if another of the deleterious effects of Abeta on long-term memory (yet to be demonstrated) was mediated by an ability to block the conversion of PrP^{C} into PrP^{Sc}. ■

Clinical perspective by Dr. Caselli, *chair of neurology at the Mayo Clinic, Scottsdale, Ariz., and professor of neurology at the Mayo Medical School, Rochester, Minn.*

Research report by Jeff Evans, clinical news editor.



Courtesy Dr. Juha Laurén/Dr. Stephen Strittmatter

Binding sites for oligomeric Abeta42 (green) colocalize with dendrites (red) on rat hippocampal neurons where cellular prion protein is located.

Mediterranean Diet May Reduce Risk of MCI and AD

BY MARY ANN MOON

Adhering to a Mediterranean diet appears to lower the risk of progressing from mild cognitive impairment to Alzheimer's disease and may cut the risk of developing MCI as well, according to a recent study.

There may also be a dose-response effect, with greater adherence to the Mediterranean diet conferring greater protection from cognitive decline, said Dr. Nikoloaos Scarmeas and his associates at Columbia University Medical Center, New York.

The researchers assessed the association between diet and MCI and AD using data from the Washington Heights–Inwood Columbia Aging Project.

The WHICAP study included comprehensive neuropsychological testing of probability samplings of Medicare beneficiaries residing in Manhattan in 1992 and 1999.

A total of 1,800 subjects who were cognitively normal at baseline were followed for approximately 4 years for the development of MCI. The investigators also followed 564 patients with MCI at baseline for the progression to AD (Arch. Neurol. 2009;66:216-25).

The Mediterranean diet is characterized by high intake of fish, vegetables, legumes, fruits, cereals, and unsaturated fatty acids, mostly in the form of olive oil; low intake of dairy products, meat, and saturated fatty acids; and regular but moderate intake of alcohol.

Greater adherence to this type of diet was associated with "a borderline trend for lower risk of developing MCI," Dr. Scarmeas and his associates said. Compared with subjects who did not adhere to the Mediterranean diet, those who reported intermediate adherence had a 17% lower risk of developing MCI; those who reported greatest adherence had a 28% lower risk.

Greater adherence to the Mediterranean diet also was associated with a lower risk of progressing to AD.

Compared with subjects who did not adhere to this type of diet, those who reported intermediate adherence had a 45% lower risk of progressing to AD; those who reported greatest adherence had a 48% lower risk, the investigators said.

The findings did not change when the data were adjusted to account for several potential confounders such as subject age, gender, ethnicity, level of education, apolipoprotein E genotype, caloric intake, and body mass index.

The investigators received support for the study through grants from the National Institute on Aging. ■