NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Exploring the Link Between Hypoxia and Amyloid Deposition

In our first column of 2009, we continue to explore the pathophysiology of Alzheimer's disease, and more specifically, how oxygen, blood flow, and energy metabolism might interact with amyloid to initiate the neurodegenerative cascade. What is the first step? When do reparatory mechanisms become pathogenic? These are issues confronted by our current studies.

RICHARD J. CASELLI, M.D.

Cerebral hypoperfusion appears to contribute to and potentially initiate amyloid-β deposition in the brain and small cerebral arteries of patients with Alzheimer's disease and cerebral amyloid angiopathy, according to the results of two separate studies.

Robert D. Bell of the University of Rochester (N.Y.) and his coinvestigators reported that the overexpression of two transcription factors that control the differentiation of cerebral vascular smooth muscle cells (VSMCs) imparts a hypercontractile phenotype to small arteries in the brain, thereby reducing cerebral blood flow and suppressing the clearance of amyloid-β, or Aβ (Nat. Cell Biol. 2008 Dec. 21 [Epub doi:10.1038/ncb1819]).

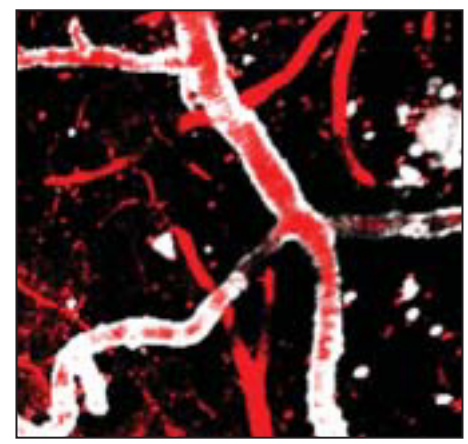
They found that in cultured VSMCs from the brains of patients with late-stage Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA), overexpression of the two interacting transcription factors—serum response factor (SRF) and myocardin (MYOCD)—promotes the expression of sterol regulatory element-binding protein-2 (SREBP2). This protein is a transcription factor that represses the expression of a protein called the low-density lipoprotein receptor–related protein-1 (LRP), which is known to be a major receptor for Aβ clearance at the blood-brain barrier and in cerebral VSMCs.

The researchers then replicated their findings in vivo in transgenic mice that model CAA. These mice received gene transfers to the subarachnoid pial cerebral arteries consisting of either the MYOCD gene or a short hairpin RNA sequence that blocks the expression of SRF. Mice that received the MYOCD gene had increased levels of endogenous Aβ42 and Aβ40 in their vessels and brain tissue, but mice that received the short hairpin RNA sequence to repress SRF gene expression had a significantly reduced cerebrovascular load of Aβ. (See image.)

These same results were again produced in a mouse model of AD in which mice spent 2 weeks in a hypoxia chamber. But the ability of these mice to clear cerebrovascular Aβ was restored to normal after they received pial transfer of the SRF-silencing RNA sequence.

The results of the second study, by Tracy O'Connor, Ph.D., of Northwestern University, Chicago, and associates, indicates that hypoxic conditions also can increase Aβ deposition in the brain by inducing a rise in levels of a key enzyme involved in the production of neurotoxic Aβ peptides (Neuron 2008;60:988-1009).

In vitro experiments demonstrated that hypoxia, or energy deprivation, initiated a translational control mechanism that increased levels of the β-site amyloid-β precursor protein-cleaving enzyme-1 (BACE1), which along with γ-secretase, produces Aβ peptides. When the researchers treated AD mouse models with inhibitors of energy metabolism, levels of BACE1 and Aβ rose. Further tests in a mouse model of amyloidosis and in brains from individuals with AD confirmed that the activation of a key protein controlling the translation of BACE1 mRNA was correlated with the increase in BACE1.



ROBERT D. BELL/ZLOKOVIC LAB/UNIVERSITY OF ROCHESTER

Amyloid-β (white) covers pial arteries of a mouse with cerebral amyloid angiopathy.

Dr. Caselli's comment: Starting with the classic neuropathology of AD, followed by the genetic insights afforded by the discovery of amyloid precursor protein mutations and other autosomal dominant causes of AD, it has long been known that amyloid plays a central role in AD pathogenesis, but its exact role is still not clear. Interfering with amyloid itself has not yielded the dramatic benefits observed in transgenic mouse models. Current therapeutic trials of amyloid antiaggregants, secretase inhibitors, and immunotherapies all aimed at preventing or clearing amyloid from the brain have yet to yield significant benefit for humans with AD. Some have posited, reasonably, that this may simply reflect that therapies are starting too late in the disease course to be effective, but others have questioned whether we have misunderstood amyloid's role altogether (see CLINICAL NEUROLOGY NEWS, December 2008, p. 10).

In the respective studies led by Mr. Bell and Dr. O'Connor, we learn that reduced delivery of oxygen, energy deprivation, or vascular restriction provokes the formation and deposition of Aβ42, the pathogenic form that characterizes AD, and is preceded, as shown by Dr. O'Connor's team, by upregulation of BACE1.

Energy failure, specifically mitochondrial failure, has been posited to play a role in nearly all neurodegenerative diseases (Curr. Alzheimer Res. 2008;5:457-68). Results from conflicting studies have questioned the often-quoted connection between cerebral circulation and AD, but there are other promising lines of evidence that suggest an association. One is the higher risk of dementia in diabetics and patients with metabolic syndrome. Diabetes has been shown to cause a failure of energy metabolism with enhanced oxidative damage in vulnerable cell and organ systems (Neurobol. Dis. 2008;30:420-9), leading to neuropathy, atherosclerosis, and other complications. Another regards the role of apolipoprotein E and other cholesterol-related genes. Others include the association of intracranial atherosclerosis and stroke with AD, the protective potential of exercise, "heart healthy" diets, and so on.

Dr. O'Connor and colleagues suggested that early-stage biochemical changes in response to energy deprivation may be ultimately amyloidogenic, but may, in the short term, serve a more immediate protective function. This is an intriguing possibility and may lead to a new perspective of the role that BACE1, amyloid, and other disease hallmarks may be playing. Neither of the studies' authors suggest that the amyloid cascade hypothesis itself is wrong, but AD pathogenesis and the role that amyloid and other factors play remain an ongoing story.■

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, senior writer.

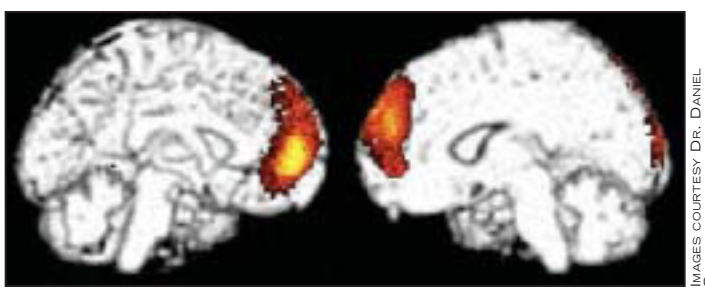
IMAGE OF THE MONTH

In an ongoing randomized trial, Dr. Daniel H.S. Silverman, Dr. Natalie L. Rasgon, and their colleagues are examining the effects of both endogenous and exogenous estrogen exposure on regional cerebral metabolism in women who were on hormone therapy (HT) at the time of recruitment and had an increased risk of Alzheimer's disease. These women either stopped or continued HT and then underwent fluorine-18 FDG-PET imaging at baseline and at 2 years. Dr. Silverman, head of the neuronuclear imaging section of the Ahmanson Biological Imaging Division at the University of California, Los Angeles, presented data at the San Antonio Breast Cancer Symposium on the first 25 women to complete the protocol.

Endogenous estrogen exposure was positively correlated most significantly with the metabolism of the precuneus area of the posterior medial cortex. "That's a part of the brain in which blood flow is decreased most significantly in early stages of Alzheimer's disease," he said.

Two years after discontinuation of HT, those women exhibited a highly significant negative correlation between the duration of endogenous exposure and the metabolism of the anterior medial cortex. "That's part of the brain that we know is affected most significantly by normal aging of the brain," he said. In contrast, women who continued on HT during the trial demonstrated a relative increase in the most anterior portion of the medial prefrontal cortex after 2 years.

In women who stopped HT, "there were two things that we saw. First of all, they didn't have that preservation of the frontal area that declines with normal aging. In addition, they experienced a significant decrease in metabolism in the inferior parietal cortex, a part of the brain that is affected very early in incipient Alzheimer's disease," he said.



IMAGES COURTESY DR. DANIEL SILVERMAN

Women on continual hormone therapy had increased metabolism in both sides of the medial prefrontal cortex.

In a parallel but unrelated trial, Dr. Silverman, along with UCLA oncologist Dr. Patti Ganz and UCLA neuropsychologist Steve Castellon, Ph.D., set out to determine the cognitive effects of chemotherapy on breast cancer patients. They conducted PET scans in 16 women who had been exposed to adjuvant chemotherapy for breast cancer—and to tamoxifen in the majority of cases. The women were studied 5-10 years after their last dose of chemotherapy and were compared with age-matched controls, who had not been exposed to chemotherapy.

Controversy exists over how much of the neurocognitive impairment that follows chemotherapy exposure (chemobrain) is directly associated with chemotherapy and how much is attributable to related factors, such as the cancer itself and precipitous menopause.

"Those who had cognitive impairment after having been exposed to chemotherapy had significantly decreased metabolism [in the inferior frontal cortex] at mental rest and substantially increased activation when performing short-term memory tasks. … these are people who start off with lower metabolism or lower activity in that part of the brain, so to perform the same task, that area of the brain has to work a lot harder to get to the same level," he said.

—Kerri Wachter