Dimebon's Effect May Challenge Amyloid Theory

BY MICHELE G. SULLIVAN

VIENNA — Dimebon—the abandoned Russian antihistamine that burst onto the Alzheimer's study scene with the only positive clinical data of 2008—may throw yet another curve ball into a research world that for years has focused almost entirely on the amyloid hypothesis.

Rather than lowering amyloid beta (Abeta) levels, as two failed investigational drugs—tramiprosate and tarenflurbil—have attempted, dimebon appears to almost immediately increase them, raising Abeta by as much as 200% in three mouse models of Alzheimer's disease (AD), Dr. Samuel Gandy reported at the International Conference on Alzheimer's Disease.

While preliminary, the findings—combined with the nearly unprecedented cognitive benefit dimebon conferred in its phase II trial—could be enough to dethrone the long-reigning amyloid hypothesis, according to Mark A. Smith, Ph.D., an AD researcher.

"This drug is clearly not targeting amyloid, but increasing it acutely," said Dr. Smith of Case Western Reserve University, Cleveland. "If you believe the dogma, therefore, you should believe that this increase will cause Alzheimer's. These results question that dogma. If this holds up, it could be enough to wound the amyloid theory, potentially mortally."

Dimebon's 2008 phase II study found that patients with mild to moderate AD who took the drug for 12 months gained about 2 points on the Alzheimer's Disease Assessment Scale-Cognition (ADAS-cog), while those taking placebo declined almost 6 points from baseline (Lancet 2008;372:207-15). A 6-month open-label extension trial found similarly positive results. Patients who completed a full 18 months of dimebon continued to show benefit on ADAS-cog. Former placebo patients who crossed over to dimebon stabilized their cognitive decline.

Dr. Gandy of the Mount Sinai School of Medicine, New York, investigated the drug's effect on amyloid in three models of the disease: cultured nerve cells, isolated synaptic terminals, and brains from mice that overexpress human amyloid.

"In every single system dimebon stimulated amyloid secretion," Dr. Gandy said in an interview. "The levels of the amyloid peptides in the interstitial brain fluid roughly doubled whenever the drug was given. If we think about the increased risk of Alzheimer's in Down syndrome patients who have a 50% increase in amyloid, this acute increase with dimebon could be significant over a period of many years of use."

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Dr. Gandy noted that similar results were obtained by John Cirrito, Ph.D., and Dr. David Holtzman of Washington University, St. Louis, who collaborated with him in studying the brains of freely moving transgenic mice that overexpress human Abeta.

Dr. Gandy suggested that this acute release may be followed by a chronic lowering of Abeta—something he is now investigating. Combined with dimebon's positive clinical data, this finding would imply that neurons benefit from dumping their intracellular amyloid load.

This is reminiscent of the evidence gathered by Dr. Holtzman's group that suggested that healthy nerve cells released more amyloid as head-injured patients began to recover, Dr. Gandy said.

The clinical and lab data highlight the essential mystery of amyloid, both researchers said. "It all seemed so simple when we discovered genes that implicated amyloid," Dr. Gandy said. "It was all amyloid toxicity and that was the end of it. But the truth is, we still don't really know what amyloid does locally. It is clear to me that amyloid beta causes the rare genetic forms of Alzheimer's, but there remains the possibility that some injurious event [e.g., calcium dysregulation or oxidative injury] is both directly neurotoxic and pro-amyloidogenic. Gary Gibson, Ph.D., of Cornell University and I have seen this in an experimental oxidative stress model, and if something like this is the case in common forms of AD, then lowering amyloid won't be sufficient. Still, I don't think we'll know that until we succeed in purging the brain of amyloid oligomers at an early age and follow the natural history of the amyloid-free brain."

Some researchers, including Dr. Smith, have contended that amyloid isn't the direct cause of AD, but a downstream product of some other dysfunction. The plaques themselves might be largely inert, or even be protecting the brain by binding and neutralizing neurotoxins.

"It could very well be that releasing Abeta is good, and that's why drugs that lower it are ineffective, or even damaging," Dr. Smith said. A wealth of recent data seems to support that idea: In the last 2 years, four antiamyloid agents have failed their phase III trials, and both active and passive immunotherapy studies have seen about a 10% rate of vasogenic brain edema associated with plaque dissolution.

Researchers are not entirely sure how dimebon works, but are honing in on mitochondrial function. A 2003 Russian study suggested that the drug blocks the induction of the mitochondrial permeability transition pore. When the pore opens, the mitochondria lose their ability to generate energy, and can take in small molecules causing them to swell and burst, in turn destroying the cells that contain them (Ann. N.Y. Acad. Sci. 2003;993:334-44).

"Medivation and Pfizer [the companies developing dimebon] also have unpublished data showing that dimebon increases neurite outgrowth, which is a metabolically demanding process, and healthy mitochondria are essential for that," Dr. Smith said.

But so far, he said, dimebon's method of action in improving cognition in AD remains unproven. "There are a lot of dots that form the shape of a mitochondria, but no one has connected them all yet."

Neither Dr. Gandy nor Dr. Smith had any relevant disclosures to make. ■

Insulin Resistance Plays Key Role

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ment, fasting insulin, and C-reactive protein, Dr. Haan said the presence of diabetes at baseline more than doubled the risk of dementia or cognitive impairment. "This translates into a population attributable risk of 19%," she said. "Nineteen percent of all these dementia cases were the direct result of type 2 diabetes."

When carried forward in accordance with the projected increases in obesity, that 19% figure means that by 2040, 24 million cases of dementia could be directly tied to type 2 diabetes, Dr. Haan said.

Unfortunately, "There are no randomized controlled trials that support the notion that we should be treating [cognitive impairment] with an antidiabetic drug," she said. Instead, the most effective method is probably to prevent obesity and insulin resistance—the two factors that most strongly influence the development of diabetes.

Suzanne Craft, Ph.D., agreed. "This current epidemic of diabetes associated with insulin resistance, in conjunction with a rapidly aging population, may foreshadow an epidemic of Alzheimer's." And while it makes sense to investigate the impact that diabetes treatment might have on cognition, an incredibly effective intervention already exists.

"Exercise is the most potent insulin-sensitizing agent we have," said Dr. Craft, a neuroscientist and Alzheimer's researcher at the Veterans Administration Puget Sound Health Care System and the University of Washington, both in Seattle. "A single bout of aerobic exercise improves insulin sensitivity for 24 hours. It's much more potent than any medication. Caloric restriction also lowers hyperinsulinemia and improves insulin sensitivity."

A large body of work now suggests that insulin resistance increases the risk of Alzheimer's by multiple mechanisms, Dr. Craft said. Far from being active only in the periphery, insulin readily crosses the blood-brain barrier and binds to receptors located throughout the brain—especially in areas of strategic importance in cognition: the hippocampus, entorhinal cortex, and frontal cortex. Once in the brain, insulin interacts with amyloid beta in several ways, increasing its intracellular clearance through insulin degrading enzyme and apparently even protecting neurons from the protein's toxic effects.

"This has been known for some time, but recent research has shown that amyloid beta may have its own independent effects on insulin signaling," Dr. Craft said. A series of experiments by William L. Klein, Ph.D., concluded that soluble oligomers of amyloid beta can remove insulin receptors from the dendritic plasma membranes of hippocampal neurons. However, she said, "If insulin was administered before the oligomeric Abeta, the dendritic spines were protected."

The study, published in February, concluded that insulin receptor signaling downregulated the oligomeric binding sites. The addition of rosiglitazone potentiated this effect, suggesting that insulin-sensitizing agents may have some role in cognitive protection (Proc. Natl. Acad. Sci. U.S.A. 2009;106:1971-6).

"Insulin appears to mitigate many of the negative effects of amyloid and regulates its clearance, while beta amyloid appears to reduce insulin signaling. So high levels of insulin in the brain can induce a brain insulin-resistance by removing the insulin receptors from the nerve cell membranes," Dr. Craft said.

She recently investigated insulin's effect on memory in a group of 33 patients with Alzheimer's or mild cognitive impairment and 59 elderly controls. The patients received placebo or five escalating doses of intranasal insulin, which travels directly into the central nervous system along the olfactory and trigeminal vasculature. Cognition was tested 15 minutes after each treatment. "We saw a 50% improvement in memory compared to baseline with the highest dose," Dr. Craft said (J. Alz. Dis. 2008;13:323-31).

Insulin also affects vascular function in the brain. "It's very well known that insulin resistance is accompanied by peripheral vascular dysfunction, but the understanding that this may also manifest in the brain is very new and potentially important."

She saw this in a recent study of 196 brains (71 with dementia). The brains were divided into four groups: normal; diabetic without dementia; diabetic with dementia; and dementia without diabetes (Arch. Neuro. 2009;66:315-22).

"We saw a surprising pattern when we looked at plaques and tangles: The brains of the patients with dementia but no diabetes had a high load, as anticipated, but the brains of diabetic patients with dementia had a plaque load that was similar to the normal controls."

The patients with both dementia and diabetes did, however, show high levels of microvascular lesions, which were absent in the other groups. "The volume of the lesions is small, so they are almost certainly not directly responsible for the cognitive impairment, but this finding may point to some broader based vascular dysfunction," Dr. Craft said. ■