In Alzheimer Research, Glucose Metabolism Moves to Center Stage

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Areas or patterns of reduced glucose metabolism are often seen in brain scans of patients with Alzheimer disease and other dementias. Now, a growing body of evidence suggests that glucose hypometabolism may be more than just a biomarker on brain scans: it may be a key player in dementia pathology.

At the Society for Neuroscience’s recent annual meeting, several research teams presented data on mechanisms that may hamper brain energy metabolism in Alzheimer disease—and potentially contribute to cognitive decline. At the same time, clinical researchers are exploring ways to slow or prevent dementia using drugs and lifestyle modifications typically prescribed for metabolic disorders like diabetes or obesity. These lines of inquiry have taken on new urgency as several amyloid-targeting therapies for Alzheimer disease pathology have failed in clinical trials, leading to questions about whether the so-called amyloid hypothesis may be flawed.

“We’ve known for probably 20-plus years that type 2 diabetes seems to increase risk for Alzheimer disease,” Macauley said. “We’re still trying to understand why.”

Evidence that insulin resistance within the brain may contribute to Alzheimer disease pathology has led some scientists to suggest that Alzheimer disease may be a brain-specific “type 3 diabetes.” Others have focused on the way type 2 diabetes might produce Alzheimer-related brain changes.

Diabetes clearly contributes to vascular dysfunction such as atherosclerosis, which increases stroke risk, said Jose Luchsinger, MD, MPH, vice chair for clinical and epidemiological research at the Columbia University Irving Medical Center in New York City. In turn, stroke may play a role in certain forms of dementia. However, on most brain autopsy studies, patients with diabetes don’t have more of the amyloid plaques and tau tangles associated with Alzheimer disease than people without diabetes, he said.

“We’re starting to try to understand how [brain glucose metabolism] could be more of a causal player in the disease, and a modifiable player,” said Shannon Macauley, PhD, an assistant professor at the Alzheimer’s Disease Research Center at Wake Forest School of Medicine in Winston-Salem, North Carolina.

The Diabetes Link
Observational studies have long suggested that patients with diabetes have an elevated risk of developing Alzheimer disease and other forms of dementia. But the nature of this relationship isn’t clear.

“People with diabetes have an increased rate of Alzheimer disease,” Luchsinger said. He and his colleagues are currently studying how, but he suspects that diabetes and prediabetes affect the brain through multiple pathways, some of which may be improved by drug therapy, including neurovascular insult.

“At the very least, diabetes creates a hit that makes the brain more susceptible to other conditions of aging, such as Alzheimer disease or neurodegeneration in general,” he said.

Sleep is one pathway that may contribute. Sleep disturbances are a common problem for patients with diabetes, and people with poor sleep also have a higher risk of developing Alzheimer disease. The reverse is also true: the development of plaques and tangles negatively impacts sleep, according to Macauley.

“We decided to add one more piece of the puzzle to ask whether changes in metabolism were sufficient to disrupt sleep,” she said of a recent study presented at the neuroscience meeting. Inducing either high or low blood glucose in mouse models of Alzheimer disease caused the animals to sleep less and, tellingly, the effects were exacerbated in animals with more β-amyloid or tau pathology, she said.

Macauley described the interrelationship between sleep loss and Alzheimer pathologies as an “additive or synergistic downward spiral for the brain.” As she continues to study these interactions, she’s also investigating whether diabetes medications or sleep aids might improve sleep in animal models of Alzheimer disease, or

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at least prevent sleep loss from exacerbating the disease.

**All Roads Lead to Metabolism**

Differences in brain energy metabolism could help to explain why the rare genetic variant *apolipoprotein E* ε2 (*APOE2*) allele protects people from developing Alzheimer disease and why another variant, *APOE4*, increases dementia risk. Recent mouse studies suggest *APOE2* supercharges brain glucose metabolism, while *APOE4* appears to do the opposite.

In 2018, an analysis of proteins produced in the brains of mice that had been modified to express 2 copies of human *APOE2*, *APOE3*, or *APOE4* found major differences in glucose metabolism and synaptic function depending on which of the variants were expressed. A 2019 follow-up study from the same research team showed that glycolysis—the first step in converting glucose to energy—was much more robust in *APOE2* mouse brain cells than in brain cells from *APOE4* mice.

The study found that as *APOE2* mice aged, they produced more of an enzyme involved in glycolysis called hexokinase, which allowed them to more efficiently produce energy from glucose. Mice with the *APOE4* allele, on the other hand, had reduced hexokinase activity over time. This is consistent with the finding that *APOE4* is associated with late-onset Alzheimer disease, said Liqin Zhao, PhD, an associate professor in the School of Pharmacy at the University of Kansas in Lawrence, and senior author of both studies.

"Basically, [the] *APOE4* brain is not as efficient as the other 2 brains in terms of utilizing of glucose," Zhao said. These deficits could starve energy-hungry brain cells, potentially contributing to cognitive impairments.

Zhao and her colleagues are now looking for ways to deliver *APOE2* into the brain as a potential Alzheimer disease treatment. They're also working to better understand how *APOE4* downregulates hexokinase and whether there are ways to mitigate that potential harm.

Researchers are also interested in how glucose is transported in the Alzheimer brain. One recent study linked reduced brain glucose metabolism with impaired glucose transport in a mouse model of the disease, and previous studies have found glucose transporter deficits in samples from patients with Alzheimer disease.

Steven Barger, PhD, a professor of geriatrics, neurobiology, and developmental sciences at the University of Arkansas for Medical Sciences in Little Rock, who led the new study, suspects that inflammation, another key player in Alzheimer disease, may impair glucose transport. "To the extent that any neuroinflammation impacts cognition, it's possible that glucose interruption may be a big component of that," he said. Barger and his colleagues are currently screening for drugs that might alleviate the glucose transporter defect.

**Testing Diabetes Therapies**

As this storyline emerges, a raft of clinical trials are testing diabetes drugs among patients with Alzheimer disease or other forms of age-related cognitive impairment. A few studies are also looking at whether metabolism-boosting lifestyle interventions like dietary modifications or exercise might delay or reduce cognitive impairments.

So far, results from diabetes drug trials have been mixed. Investigators stopped a phase 3 trial of the blood glucose-lowering drug pioglitazone in 2018 after an interim analysis failed to show that it delayed the onset of mild cognitive impairment due to Alzheimer disease. But insulin—which is essential for brain energy metabolism—and other therapies might be more promising.

Suzanne Craft, PhD, who directs Wake Forest’s Alzheimer’s Disease Research Center, presented 18-month results from a phase 2 and 3 study of nasal insulin at the Alzheimer’s Association International Conference last July. The trial tested 2 different intranasal insulin delivery devices; patients who used one model appeared to benefit, whereas patients who used another did not.

“What we’ve learned is that not all devices are created equal,” said Craft, who also co-directs the Sticht Center for Healthy Aging and Alzheimer’s Prevention at Wake Forest. She and her colleagues are currently testing intranasal insulin devices to ensure delivery into the brain, a necessary component for a planned phase 3 trial.

Luchsinger, meanwhile, is studying whether the diabetes drug metformin can keep people with mild cognitive impairment from progressing to Alzheimer disease. The drug helps to control glucose and increase insulin sensitivity and has a long track record of safety among individuals without diabetes. Other researchers are interested in the GLP-1 analogue liraglutide, which in a small 2016 trial stabilized glucose levels in patients with Alzheimer disease. Results from a larger study are expected soon.

With a dearth of treatment options, Craft and others are also turning to lifestyle interventions that may have beneficial metabolic effects in both the body and brain. Craft recently published results of a pilot crossover trial comparing a modified version of the ketogenic diet incorporating Mediterranean...
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cerebrospinal fluid. "With the ketogenic diet, we are moving the β-amyloid in a healthier direction," Craft said. Patients also had better blood flow to the hippocampus and improved body-wide insulin sensitivity. A larger trial of the modified ketogenic diet is now under way.

Craft is also exploring the benefits of exercise, which has been shown to improve cognition and insulin sensitivity in other populations, as a therapy for patients with Alzheimer disease. In Luchsinger’s view, there isn’t enough evidence yet to recommend lifestyle modifications for Alzheimer disease treatment, although he noted that a recent Finnish trial provided proof of concept that lifestyle interventions may benefit those at risk for dementia.

“I certainly think that having healthy habits, eating in a way that you keep a healthy weight, doing physical activity—it’s going to be good even if it doesn’t necessarily change Alzheimer disease,” he said. “It’s more likely to make the brain more resilient to the effects of aging.”

But Craft emphasized that a healthy lifestyle that boosts the brain’s resilience could potentially delay the onset of dementia. “There’s a lot that can be done to, at the very least, push the onset of these disorders back in time,” she said. "It would mean people have lived a good life for much longer." ■

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