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Sugar and Alzheimer's disease: a bittersweet truth

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Abstract

Reductions in brain glucose metabolism have long been associated with Alzheimer's disease. A study now demonstrates that the endothelial glucose transporter GLUT1 is vital for maintaining brain energy metabolism and vascular clearance of amyloid-β.

The brain is the most energy-demanding organ of the body and is critically dependent on a daily supply of a quarter of a pound of glucose, its main energy source, to generate the ATP it needs to function[1]. The job of delivering such a large amount of glucose across the blood-brain barrier (BBB) falls exclusively to endothelial cells lining cerebral blood vessels. Endothelial cells make up less than 1% of brain cells, but are loaded with GLUT1, a specialized transporter protein that helps glucose cross the BBB and enter the brain[2]. Defects in cerebral glucose metabolism in Alzheimer's disease (AD), the most frequent cause of dementia, have suggested that 'brain starvation' could be involved in the disease process[3]. However, proof that this mechanism, albeit plausible, could induce brain dysfunction and contribute to AD has been lacking. As reported in this issue of *Nature Neuroscience*, Winkler *et al.*[4] used mouse models to demonstrate that GLUT1 deficiency leads to profound changes in vascular, BBB and neuronal function that are particularly damaging in the setting of AD pathology. In addition to highlighting a new function of GLUT1 in vascular homeostasis, these findings establish endothelial GLUT1 as critical factor in maintaining brain health and a potential therapeutic target in AD.

Brain scans using [^{18}F]fluoro-2-deoxyglucose first revealed reductions in cerebral glucose transport and utilization in selected brain regions of AD patients[5,6]. These changes occurred early in the disease course and were also present in cognitively normal individuals at genetic risk for AD[5], suggesting a causal involvement in the disease process. Reductions in the endothelial GLUT1 transporter were subsequently found in the brains of AD patients, raising the possibility that the reduced glucose utilization was a consequence of the deficits in glucose transport across the BBB[7,8]. However, the effect of these alterations on brain function and disease process remained uncertain for over two decades. Winkler *et al.*[4] set out to answer this longstanding question using mice with a deficit in the gene encoding GLUT1 (*Slc2a1*$^{+/-}$ mice). They found that *Slc2a1* haploinsufficiency led to age-dependent reductions in vascular length, cerebral blood flow and glucose uptake, and to an increase in

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BBB permeability (Fig. 1). These vascular and metabolic alterations were associated with reduced dendritic spines in the CA1 region of the hippocampus, coupled with alterations in recognition of novel objects and nesting behavior, suggesting cognitive dysfunction. With advancing age, *Slc2a1*-deficent mice also exhibited evidence of neurodegeneration in the cortex and hippocampus. These observations reveal an unexpected effect of endothelial GLUT1 deficiency on the brain and its vessels that results in brain dysfunction and neurodegeneration.

On the basis of the reported reduction in GLUT1 in AD brains, Winkler *et al.*[4] sought to examine the effect of GLUT1 deficiency on AD pathology. To this end, they crossed *Slc2a1*-haploinsufficient mice with mice overexpressing the amyloid precursor protein containing the Swedish mutation (APP^{Sw} mice), which develop amyloid plaques, a hallmark of AD pathology. They found that *Slc2a1* deficiency exacerbated the alterations in vascular structure, function and BBB permeability observed in APP^{Sw} mice. The brain accumulation of amyloid-β (Aβ), a pathogenic factor in AD, was enhanced as well, an effect related to reduced brain Aβ clearance caused by suppression of the vascular Aβ transporter lipoprotein receptor-1 (LRP1; Fig. 1). Furthermore, *Slc2a1* deficiency worsened the neuronal dysfunction, CA1 spine loss and behavioral deficits in APP^{Sw} mice.

At variance with the findings in human disease, endothelial GLUT1 and glucose uptake were not markedly suppressed in APP^{Sw} mice, and certainly less so than in *Slc2a1* mice. Yet APP^{Sw} mice displayed vascular, BBB, neuronal and behavioral alterations similar to those of *Slc2a1* mice. Thus, GLUT1 deficiency does not drive the vascular phenotype in APP^{Sw} mice, and other factors, such as Aβ, must be responsible for their vascular and cognitive alterations. However, *Slc2a1* deficiency greatly exacerbated the dysfunction and damage in APP^{Sw} mice. Thus, the reduction in endothelial GLUT1 observed in AD must have the potential to act synergistically with AD pathology to enhance its damaging effects on the brain and promote the progression of the dementia.

What causes the reductions in glucose utilization in AD? This has emerged as a sensitive biomarker of AD and has become an important metric for staging disease progression[9]. Reductions in glucose utilization in the posterior cingulate and parietal-temporal cortices occur relatively early in the disease and are associated with increased cerebrospinal fluid tau, a neurofilament protein that is abnormally phosphorylated in AD, and hippocampal atrophy[10]. One possibility is that the hypometabolism is secondary to reduced neuronal activity and, consequently, reduced energy expenditure. However, the report by Winkler *et al.*[4] suggests an alternative explanation. The GLUT1 reduction could reduce glucose uptake and limit the brain's supply of energy, which, akin to a kink in the fuel line of a combustion engine, could impair neuronal activity and, in the long run, result in neurodegeneration. Deficits in neuronal energy metabolism have long been implicated in AD[11], and efforts to provide alternative energy substrates such as dietary ketones to the brain or to enhance neuronal glucose uptake by intranasal insulin have met with some success[3,12,13]. This scenario raises the possibility that, in AD, the brain is starved of glucose and generates ATP from oxidation of ketone bodies, as suggested by early studies of cerebral metabolism[1]. A similar situation is found in patients with *SLC2A1* deficiency, a rare genetic disease

associated with prominent neurological deficits, in whom a ketogenic diet is highly beneficial[14].

Could GLUT1 be used to develop new therapeutic interventions in AD? If a reduction in endothelial GLUT1 enhances AD pathology, it is conceivable that restoring GLUT1 levels could ameliorate brain dysfunction and damage in AD. To begin to address this question, Winkler *et al.*[4] performed adenoviral gene transfer in APP^{Sw} mice deficient in *Slc2a1*. They found that restoration of GLUT1 in the hippocampus greatly reduced local Aβ levels. Similar results were obtained with viral gene transfer of LRP1, the Aβ vascular transport protein suppressed by GLUT1 deficiency. Although the authors did not demonstrate rescue of neuronal function and behavior, the findings provide proof of principle that upregulation of GLUT1 clears the brain of amyloid and could have beneficial effects.

Little is known about the mechanism causing GLUT1 dysregulation in AD. GLUT1 expression is controlled by hypoxia-inducible factor 1 (HIF1α,β). Given that HIF1α is down-regulated in AD[15], it is conceivable that HIF1α suppression leads to reduced GLUT1 expression. However, earlier studies have indicated that *SLC2A1* mRNA is not reduced in AD, implicating post-translational mechanisms[8]. Thus, further studies on the molecular bases of GLUT1 reduction are needed to provide some indication of how to counteract it.

Irrespective of the many questions outstanding, the data of Winkler *et al.*[4] demonstrate a multifaceted role of glucose transport in the maintenance of brain structure and function, and unveil a damaging interaction with AD pathology. This may open new therapeutic avenues for this devastating neurodegenerative disease.

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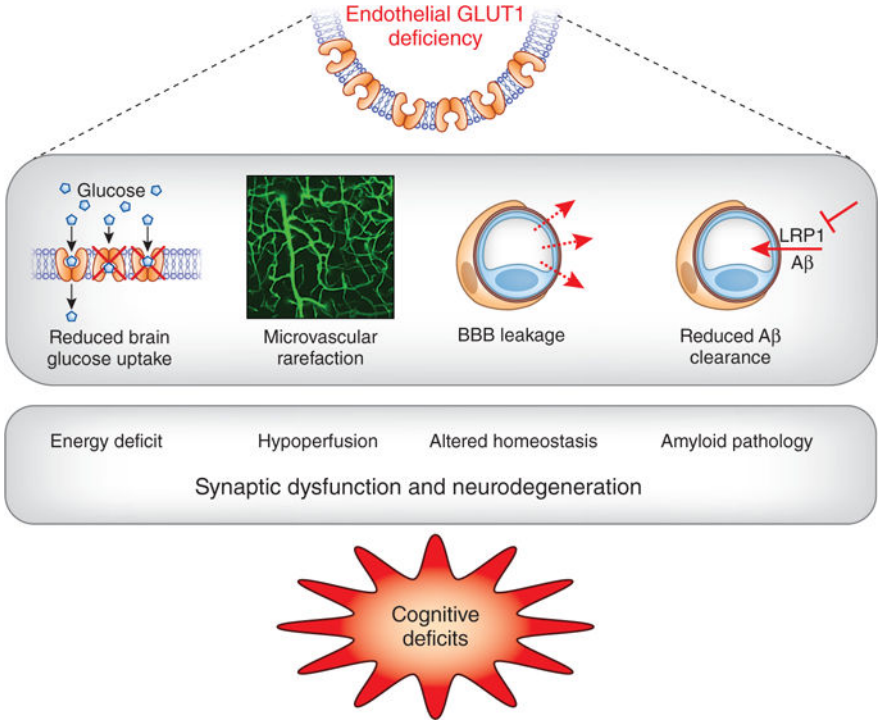

Figure 1.

Mechanisms of brain dysfunction and damage caused by GLUT1 deficiency. Endothelial GLUT1 deficiency leads to reduced brain glucose transport, vascular rarefaction and disruption of the BBB, as well as reduced Aβ clearance by suppressing vascular LRP1 expression. These events result in energy deficit, reduced cerebral blood flow (hypoperfusion), altered homeostasis of the brain microenvironment and enhanced amyloid pathology. The resulting synaptic dysfunction and neurodegeneration in turn lead to cognitive deficits.