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Featured Article

Evidence for brain glucose dysregulation in Alzheimer's disease

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Abstract

Introduction: It is unclear whether abnormalities in brain glucose homeostasis are associated with Alzheimer's disease (AD) pathogenesis.

Methods: Within the autopsy cohort of the Baltimore Longitudinal Study of Aging, we measured brain glucose concentration and assessed the ratios of the glycolytic amino acids, serine, glycine, and alanine to glucose. We also quantified protein levels of the neuronal (GLUT3) and astrocytic (GLUT1) glucose transporters. Finally, we assessed the relationships between plasma glucose measured before death and brain tissue glucose.

Results: Higher brain tissue glucose concentration, reduced glycolytic flux, and lower GLUT3 are related to severity of AD pathology and the expression of AD symptoms. Longitudinal increases in fasting plasma glucose levels are associated with higher brain tissue glucose concentrations.

Discussion: Impaired glucose metabolism due to reduced glycolytic flux may be intrinsic to AD pathogenesis. Abnormalities in brain glucose homeostasis may begin several years before the onset of clinical symptoms.

Keywords: Glucose; Insulin resistance; Alzheimer's disease; GLUT3; GLUT1; Neuritic plaque; Neurofibrillary tangles; Mass spectrometry; Glycolysis

1. Introduction

Although numerous epidemiological studies indicate that peripheral insulin resistance and diabetes are risk factors for Alzheimer's disease (AD) [1–3], it is not known whether brain glucose dysregulation is a key feature of AD and is related to severity of AD pathology or symptom

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expression [4,5]. Previous studies have shown that several components of the insulin signaling pathway are abnormal in AD brains relative to controls, including genes encoding insulin, IGF-1, and IGF-2 peptides and their receptors [6–10]. Because these abnormalities appear to be a common feature of both type-1 and type-2 diabetes, the term "type-3 diabetes" was proposed to describe brain-specific abnormalities in insulin signaling associated with AD [11,12]. Taken together, the large body of evidence implicating abnormal insulin signaling in AD has led to clinical trials targeting these abnormalities in patients with mild cognitive impairment and AD [13–15]. However, it is well recognized that glucose transport from the peripheral circulation across the blood-brain barrier and capillary endothelial cells into the interstitial fluid and brain tissue are largely insulin-independent processes [16,17]. Similarly, the transport of glucose across the cell membrane into neurons is largely independent of insulin [18]. Although ^{18}F-deoxyglucose positron emission tomography (^{18}FDG-PET) studies have shown reduced brain glucose uptake in regions vulnerable to AD pathology [19–22], it is unclear whether an overall failure of regulation of brain glucose metabolism is a key etiopathogenic factor in AD and whether abnormalities of brain glucose homeostasis in AD are related to peripheral glucose concentration. Answering these questions is critical to establishing whether central glucose homeostasis is a potential target for disease-modifying treatments in AD.

In this study, we asked the following main questions:

1. Is brain tissue glucose concentration altered in AD?
2. What is the relationship between brain tissue glucose concentration and severity of AD pathology?
3. What are plausible molecular mechanisms underlying abnormalities of brain glucose homeostasis in AD?
4. What is the relationship between trajectories of blood glucose concentration during life and brain tissue glucose levels measured at death?

Our results provide the first evidence for brain glucose dysregulation as a critical event in AD pathogenesis that closely reflects both severity of AD pathology and the expression of symptoms.

2. Methods

2.1. Participants

The Baltimore Longitudinal Study of Aging (BLSA) is a prospective, ongoing cohort study of community-dwelling volunteer participants in Baltimore that began in 1958 and has been described in detail previously [23,24]. Historically, participants underwent extensive biomedical examination and neuropsychological testing every 2 years. From 2003, participants under age 60 years are assessed every 4 years; those aged 60 to 79 years every 2 years and participants aged 80 years and older are assessed annually. Written informed consent was obtained at each visit, and the study was approved by the local institutional review board and the National Institute on Aging. The participants in this report were from the autopsy program of the BLSA that was initiated in 1986 and has been described previously [25]. They provided data on concentrations of brain tissue glucose and the glycolytic amino acids, serine, glycine, and alanine ($N = 43$; from the middle frontal gyrus [MFG], inferior temporal gyrus [ITG], and cerebellum), as well as proteomic data from the MFG ($N = 47$). The mean age at death in the sample was 86.6 ± 9.5 years (range 62.9–99.2). As reported previously, the autopsy subsample is not significantly different from the BLSA cohort as a whole in terms of the rates of dementia and clinical stroke [26].

2.2. Cognitive status

At each assessment, participants underwent a battery of neuropsychological testing. Clinical and neuropsychological data were reviewed at consensus case conferences if they made four or more errors on the Blessed Information Memory Concentration test, if their Clinical Dementia Rating score was equal to or greater than 0.5, or if concerns were raised about their cognitive status. In addition, all participants were evaluated by case conference on death or withdrawal. The diagnoses of dementia and AD were based on the Diagnostic and Statistical Manual-III-R [27] and the National Institute of Neurological and Communication Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria [28], respectively.

2.3. Neuropathological studies

Postmortem brain examinations were performed by an experienced neuropathologist (J.C.T.). Assessment of neuritic plaques and neurofibrillary tangles using Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [29] and Braak criteria [30], respectively, have been described previously [31]. We have previously described the clinico-pathological features of BLSA participants categorized as "asymptomatic Alzheimer's disease (ASYMAD)" after neuropathological assessment at death [32]. Briefly, these individuals have significant AD neuropathology at autopsy, but without evidence for cognitive impairment during life, as assessed by longitudinal cognitive evaluations during their BLSA research visits.

2.4. Plasma glucose measurement

Plasma glucose measurements were obtained from venous blood samples after an overnight fast by the glucose-oxidase method as described previously [33]. We used all available longitudinal plasma glucose data (445 observations, mean follow-up interval. 19.1 years). We excluded 10 data points where fasting plasma glucose values were beyond three standard deviations from the mean value.