ELSEVIER

Neurobiology of Aging 32 (2011) 1942–1948

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease

Natalie L. Rasgon [a,*], Heather A. Kenna [a], Tonita E. Wroolie [a], Ryan Kelley [b], Daniel Silverman [c], John Brooks [d], Katherine E. Williams [a], Bevin N. Powers [a], Joachim Hallmayer [e], Allan Reiss [b]

[a] *Stanford Center for Neuroscience in Women's Health, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, United States*

[b] *Center for Interdisciplinary Brain Sciences Research, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, United States*

[c] *Department of Nuclear Medicine, University of California, Los Angeles, United States*

[d] *Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, United States*

[e] *Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, United States*

Received 30 May 2009; received in revised form 14 September 2009; accepted 8 December 2009
Available online 23 December 2009

Abstract

Insulin resistance (IR) is the main pathological condition underlying vascular disorders, such as diabetes and cardiovascular disease, which are well established risk factors for cognitive decline and Alzheimer disease (AD). Hippocampal atrophy has been associated with cognitive decline, but little is known about the influence of IR on hippocampus integrity in non-diabetic, cognitively intact individuals. Herein, 50 women ages 50–65, current users of hormone therapy, underwent magnetic resonance imaging, cognitive testing, and homeostatic assessment of insulin resistance (HOMA-IR), as part of a longitudinal study examining brain structure and function in postmenopausal women at risk for AD. Results demonstrated a significant negative relationship between HOMA-IR and right and total hippocampal volume, overall cognitive performance, and selective tests of verbal and non-verbal memory. The main effect of HOMA-IR on brain structure and cognition was not altered by the presence of APOE-ε4 allele or by reproductive history, such as duration of endogenous and exogenous estrogen exposure. These results suggest that IR in middle-aged individuals at risk for AD may be biomarker for dementia risk.
© 2009 Elsevier Inc. All rights reserved.

Keywords: Insulin resistance; Postmenopausal women; Alzheimer's disease; Hippocampal volume; APOE-ε4; Dementia risk

1. Introduction

Vascular illnesses are well established as risk factors of cognitive decline, dementia and Alzheimer disease (for review, please see Craft, 2009). Insulin resistance (IR) is the main pathological condition underlying vascular disorders, such as diabetes, obesity and cardiovascular disease. The IR syndrome occurs when tissues become unresponsive to the effects of insulin and selectively affects insulin's actions in the peripheral tissues and in the central nervous system (CNS). IR, a.k.a. "pre-diabetes", is also a causal factor in most cases of type 2 diabetes mellitus (DM2). IR may initially be manifested by glucose intolerance for years prior to the onset of overt diabetes, as the pancreas is able to compensate by increased secretion of insulin to maintain normal glucose levels. Over time, the degree of IR increases as insulin secretion by pancreatic cells is reduced, resulting in DM2. Several converging lines of evidence support the notion of a worsened glycemic control/IR with advancing age (for review, please see Yaffe, 2007).

IR has been suggested in the pathophysiology of a number of major somatic and neuropsychiatric diseases. Long-standing (especially poorly controlled) glycemic control has

* Corresponding author at: Stanford University, 401 Quarry Road, Stanford, CA 94305-5723, United States. Tel.: +1 650 724 6689; fax: +1 650 724 3144.
E-mail address: nrasgon@stanford.edu (N.L. Rasgon).

0197-4580/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2009.12.005

been shown to cause both diffuse and focal changes in the brain, exhibited as cognitive decline (Craft, 2009). In addition to its peripheral effects, insulin has significant effects in the CNS. For example, insulin affects hypothalamic structures involved in body weight regulation (Porte and Woods, 1981), and it influences hippocampal-mediated memory processing (Craft, 2005; Craft et al., 1999a,b, 2000, 2003; Craft and Watson, 2004; Marfaing et al., 1990). Notably, CNS insulin receptors are predominantly located in the hippocampus and adjacent limbic structures (Lannert and Hoyer, 1998; Unger et al., 1991).

We previously postulated that long standing IR in persons with affective disorders may lead to hippocampal neuronal damage and subsequently increase risk for Alzheimer's disease (AD) (Rasgon and Jarvik, 2004). Further, hyperglycemia is associated with accelerated formations of advanced glycation end products that may cross-link amyloid and tau protein facilitating intracellular plaque and extracellular neurofibrillary tangle formation, all of which are hallmark lesions in AD (Craft, 2009). Conversely, repeated hypoglycemic events are associated with cerebral atrophy, white matter lesions, and persistent cognitive impairment (Craft, 2009).

Hippocampal atrophy has been suggested as a putative biomarker of impending cognitive decline and a predictor of AD (Hampel et al., 2008). Numerous studies have shown marked reductions in hippocampal volumes on magnetic resonance imaging (MRI) in patients with overt AD compared with healthy elderly individuals (for example, de Leon et al., 2004; Hampel et al., 2008). Patients with mild cognitive impairment, who are at high risk of developing AD, also have smaller hippocampal volumes than healthy elderly people (de Leon et al., 2004; Hampel et al., 2008).

There is paucity of data examining the relationship between non-diabetic IR or overt DM2 and hippocampal structure in older, non-demented adults. A 6-year follow-up MRI study of normal aging subjects found that increased circulatory glucose concentrations, as evidenced by elevated glycated hemoglobin A, was associated with greater rate of an overall brain atrophy (Enzinger et al., 2005). Similarly, in a large cross-sectional evaluation of cognitively intact older adults with and without DM2, DM2 was associated with greater overall brain atrophy (Kumar et al., 2008). den Heijer et al. (2003) described significantly greater hippocampal and amygdala volumes atrophy in non-demented older adults with DM2 in comparison to non-diabetic persons.

To date, no study has examined the effects of IR on hippocampal volume and cognitive performance in non-diabetic persons *at risk* for AD (by virtue of carrying apolipoprotein ε-4 or having family history of AD). This issue was examined in the cross-sectional data that follows, which represent part of a larger longitudinal study evaluating cerebral metabolism, brain structure, and cognitive performance in cognitively intact, postmenopausal women at risk for AD.

2. Methods

2.1. Study participants and screening procedures

The study was approved by the Stanford University Institutional Review Board and all participants provided written informed consent. The sample consisted of 50 physically healthy, cognitively intact Caucasian postmenopausal women who were participating in a larger study of brain changes during postmenopause. All participants were users of hormone therapy at the time of study participation.

The screening visit included psychiatric, physical, and neurological examination to determine eligibility for the study. All participants were screened for dementia using the Mini Mental Status Exam, and for Parkinson disease using the motor examination (items 18–31) of the Unified Parkinson's Disease Rating Scale (Fahn et al., 1987). The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder-IV was used to determine that no participant met criteria for current major mood or anxiety disorder, as well as to exclude history of psychosis. The 17-item Hamilton Depression Rating Scale (HDRS-17) was also administered by a trained clinical interviewer to rule out clinically significant symptoms of depression. Exclusion criteria included evidence of current depression as determined by a score of >8 on HDRS-17, history of drug or alcohol abuse, contraindication for MRI scan (e.g., metal in body, claustrophobia), history of mental illness (excluding mood disorders), or significant cognitive impairment, as evidenced by impairment in daily functions and/or MMSE $\leq$27 (Folstein et al., 1975), history of myocardial infarction within the previous year or unstable cardiac disease, significant cerebrovascular disease, as evidenced by neurological examination, uncontrolled hypertension (systolic BP >170 mmHg or diastolic BP >100 mmHg), history of significant liver disease, clinically significant pulmonary disease, type 1 or type 2 diabetes, or cancer. Subjects were also excluded if they used drugs with potential to significantly affect psychometric test results, including centrally active beta-blockers, narcotics, clonidine, anti-Parkinsonian medications, antipsychotics, benzodiazepines, systemic corticosteroids, medications with significant cholinergic or anticholinergic effects, anticonvulsants, or warfarin.

After the screening visit, eligible subjects underwent measurement of morning fasting plasma insulin (FPI) and glucose (FPG), magnetic resonance imaging (MRI), cognitive testing, and genotyping for apolipoprotein E (APOE). The homeostatic assessment of insulin resistance (HOMA-IR) was calculated using the standard formula of HOMA-IR (mM/L × μU/ml) = fasting glucose (mM/L) × fasting insulin (μU/ml)/22.5 (Matthews et al., 1985). HOMA-IR is highly correlated with direct estimates of insulin resistance obtained via the euglycemic clamp method (Hermans et al., 1999). In addition, complete reproductive history was taken on all subjects, including age at menopause, type of menopause

Download English Version:

https://daneshyari.com/en/article/6810142

Download Persian Version:

https://daneshyari.com/article/6810142

Daneshyari.com