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

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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.

Keywords

insulin resistance; postmenopausal women; Alzheimer's disease; hippocampal volume; APOE-ε4; dementia risk

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Disclosure Statement

None of the authors have any actual or potential conflicts of interest.

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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 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., 2003; Craft et al., 1999a; Craft et al., 2000; Craft et al., 1999b; 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

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 ≤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 $\text{HOMA-IR} (\text{mM/L} \times \mu\text{U/ml}) = \text{fasting glucose (mM/L)} \times \text{fasting insulin} (\mu\text{U/ml}) / 22.5$ (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 (natural or surgical), age at menarche, length of hormone therapy use, and type hormone therapy.

Magnetic Resonance Imaging

High-resolution magnetic resonance images were obtained on a 1.5 Tesla General Electric Signa unit as a series of 124 1.5-mm coronal brain slices using a 3D fast spoiled gradient

recalled echo with the following parameters: TR: minimum, TE: minimum, 15° flip angle, voxel size=0.98 × 0.98 × 1.5mm. The images were hand processed to remove scalp, skull, and meninges. Brain volumes were calculated using the program *FSL* (University of Oxford, <http://www.fmrib.ox.ac.uk/fsl>). The hippocampal delineation procedure was adapted from existing protocols (Kates et al., 1997). Using the software *BrainImage Java* (Stanford University, <http://cibsr.stanford.edu/tools>), one experienced blinded rater traced the exterior boundaries of each hippocampus. (Previous inter-rater reliability with “gold standard” datasets was established with intraclass correlation coefficient > 0.90.)

Cognitive Assessment

The cognitive test battery included measures considered to assess verbal and non-verbal cognitive function, as well as measures of general cognitive functioning. The following tests were administered: The Auditory Consonant Trigrams (ACT) as a measure of verbal memory, attention, and information processing; the Benton Visual Retention Test (BVRT) as a measure of nonverbal attention and memory; the Buschke-Fuld Selective Reminding Test (BSRT) as a measure of verbal learning/retrieval; the Rey-Osterrieth Complex Figure Test (RCFT) as a measure of nonverbal delayed memory; the MMSE as a measure of overall cognitive functioning; and the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) as measures of general intelligence and overall cognitive functioning. Analyzed outcome variables included ACT total score, number of perseverations, and number of sequencing errors, BVRT total score and number of errors, BSRT total score, number of perseverations, and number of deletions, RCFT immediate and delayed recall scores, and MMSE score. Standardized scores on the WASI vocabulary and matrix reasoning subtests were used to calculate the Full Scale Intellectual Quotient (WASI-FSIQ).

Statistical Analysis

Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL). Linear regression modeling was used to test the primary hypothesis that HOMA-IR would predict left, right, and total hippocampal volume (corrected for total brain volume), as well as cognitive performance. For outcome variables found to be correlated with age, age was included as a covariate in subsequent multiple regression analyses. Multiple regression analyses were also conducted on all outcome variables with genetic risk (APOE-ε4 carriership) as a covariate. Given that all subjects were postmenopausal women using estrogen hormone therapy, multiple regression analyses were also performed to assess the possible confounding effects of menopause-related reproductive variables, such as duration of endogenous estrogen exposure (e.g. length of reproductive life, or age at menopause minus age at menarche), and duration of exogenous estrogen exposure (duration of hormone therapy (HT) in the relationship of the hippocampal and cognitive performance variables found to be significantly related to HOMA-IR.

3. RESULTS

Demographic and clinical characteristics of the 50 subjects are presented in Table 1. All subjects had MMSE within the normal range for cognitively intact persons of their same age and level of education. Age was not significantly correlated with HOMA-IR ($r=.235$, $p=.100$), left hippocampal volume ($r=-.146$, $p=.313$), or total hippocampal volume ($r=-.230$, $p=.107$), but a strong trend was noted for correlation between age and right hippocampal volume ($r=-.277$, $p=.051$). As BMI is generally highly correlated with HOMA-IR and was observed to be highly correlated in the present sample ($r=.484$, $p<.001$), Pearson correlations were used to test for associations of BMI with hippocampal volume and cognitive performance, with results showing no significant or trend relationships. With respect to

cognitive performance, age was significantly correlated with ACT perseverations ($r=-.345$, $p=.014$) and BSRT perseverations ($r=-.327$, $p=.020$), but not with any other cognitive outcome variables.

HOMA-IR and Hippocampal Volume

Multiple regression analysis with HOMA-IR and total brain volume as independent variables and left, right, or total hippocampal volume as the dependent variable revealed a significant main effect of HOMA-IR on right hippocampal volume ($t=-2.768$, $p=.008$) and total hippocampal volume ($t=-2.367$, $p=.022$). Given the strong trend correlation between age and right hippocampal volume, age was included with HOMA-IR and total brain volume in a subsequent multiple regression analysis on right hippocampal volume, with results showing a continued significant main effect for HOMA-IR ($t=-2.385$, $p=.021$) but no significant main effect for age ($t=-1.423$, $p=.162$). Inclusion of APOE- $\epsilon 4$ carriership as a covariate likewise showed a continued significant main effect for HOMA-IR ($t=-2.619$, $p=.012$ and $t=-2.212$, $p=.032$, respectively), with no main effect for APOE- $\epsilon 4$ on right and total hippocampal volume ($t=0.876$, $p=.386$ and $t=1.096$, $p=.279$, respectively). Figure 1 displays a scatterplot between HOMA-IR and right hippocampal volume corrected for total brain volume.

HOMA-IR and Cognitive Functioning

Mean scores, standard deviations, and regression results are summarized in Table 2. Results indicated a significant association between HOMA-IR and both ACT and BVRT scores. In contrast, there were no associations of HOMA-IR with BSRT and RCFT scores. HOMA-IR was significantly correlated with MMSE scores, as well as WASI-FSIQ scores and its subtests. Figure 2 displays a scatterplot between HOMA-IR and MMSE. As age was observed to significantly correlate with ACT perseverations, it was included as a covariate in a subsequent multiple regression model of HOMA-IR on ACT perseverations, with results showing a significant main effect of age ($t=2.032$, $p=.048$) and a continued significant main effect of HOMA-IR ($t=2.360$, $p=.022$).

Inclusion of APOE- $\epsilon 4$ carriership in subsequent multiple regression models showed no significant main effect for the presence of APOE- $\epsilon 4$ allele on any of the cognitive performance variables, while HOMA-IR continued to have the same significant main effects as outlined in Table 2.

Reproductive Variables, HOMA-IR, Hippocampal Structure and Cognitive Functioning

Subsequent multiple regression analyses aimed at assessing the possible confounding effects of the reproductive variables (endogenous and exogenous estrogen exposure) revealed no significant main effects for either reproductive variable on hippocampal volumes or cognitive variables (data not shown). At the same time, the main effect of HOMA-IR on right and total hippocampal volume remained significant in each model ($t=2.731$, $p=.009$ and $t=2.419$, $p=.020$ for the right hippocampus, respectively; $t=2.035$, $p=.048$ and $t=2.270$, $p=.028$ for total hippocampus, respectively), as well as for MMSE score ($t=2.028$, $p=.048$). Duration of endogenous estrogen exposure had a significant main effect on WASI-FSIQ scores ($t=2.413$, $p=.020$), which was independent of the main effect of HOMA-IR on WASI-FSIQ scores ($t=-.3784$, $p<.001$). Similar results were found with respect to the WASI matrix reasoning subtest ($t=3.018$, $p=.004$, and $t=-4.139$, $p<.001$, respectively) and the WASI vocabulary subtest ($t=2.031$, $p=.048$, and $t=-3.887$, $p<.001$, respectively).

4. DISCUSSION

The main purpose in identifying modifiable risk factors for AD, such as IR, DM2 and cardiovascular disease, is to delay or even prevent neurodegeneration. Our results support this notion by postulating negative effects of IR on hippocampal volumes and cognitive performance in cognitively intact middle aged women at risk for AD. The importance of studying effects of IR on brain structure and cognitive performance is emphasized by the high prevalence of IR in the general population and its growth in direct association with rates of obesity.

IR might be a link between disorders of mood and cognition, as it may be leading to neuronal loss in the hippocampus due to the high concentration of insulin receptors in that region (Rasgon and Jarvik, 2004). As summarized by Craft (2009), insulin transport across the blood brain barrier is reduced by prolonged peripheral hyperinsulinemia, which may help explain the observations of reduced insulin and brain insulin-signaling markers in the cerebrospinal fluid of patients with AD. In our sample of women at risk for AD, measures of IR were peripheral, consistent with other human studies using peripheral measures of IR as a proxy for central IR state (for example, (Craft et al., 1993; Craft et al., 1998)).

It also appears that IR specifically affects the hippocampus, as we did not find an association between IR and total brain volume ($r=.137$, $p=.342$). Similarly, Convit et al. pointed to hippocampus as the main target for IR, which can be explained by a preponderance of insulin receptors in that brain region (Convit et al., 2005). In this sample IR was associated with verbal (ACT) and non-verbal (BVRT) measures with a brief one-trial stimulus presentation, but not with verbal learning/retrieval (BSRT) or nonverbal delayed memory (RCFT) where stimulus presentation occurred over a longer period of time. It is possible that IR may affect the very earliest and initial encoding process, namely acquisition of information, which may be an early indication of reduced learning capacity. Reduced learning capacity and defective encoding in patients with AD may contribute to the typical impairment of delayed memory (for example, please see Lowndes et al., 2008; Pierce et al., 2008). Therefore, it is plausible that observed differential performance in selective cognitive domains in relation to worsening glucose regulation/IR represent the first subtle changes in memory among middle-aged individuals at risk for dementia, which may further deteriorate with age and progression of metabolic dysfunction.

In line with our findings, Convit et al. reported a significant correlation of impaired glucose tolerance (as measured by the intravenous glucose tolerance test) with both immediate and delayed paragraph recall, as well as hippocampal atrophy, in a sample of 30 non-diabetic, non-demented middle-aged and elderly men and women (ages 53–89, mean age of 69) (Convit, et al., 2003). Our findings extend those of Convit et al. (2003), as they pertain to a larger sample ($n=50$) that is more homogenous with respect to age, gender, and other clinical characteristics, such as risk for dementia.

IR has also been associated with decreases in measures of global cognitive functioning (such as the MMSE) in several large population-based studies (Kuusisto et al., 1993; Stolk et al., 1997) (Kalmijn et al., 1995; Vanhanen et al., 1998). In this sample there was a decrease in both MMSE and WASI-FSIQ scores with increasing IR. In addition, both tests were highly correlated with each other ($r=.374$, $p=.008$). The WASI-FSIQ score is based on an abbreviated IQ measure that uses only two subtests, which are considered markers of crystallized intelligence; that is, they tend not to decline (at least not much) with decline in cognition, particularly the verbal subtest. Further, WASI-FSIQ is highly correlated with the full scale IQ obtained in the Wechsler Adult Intelligence Scale-III (The Psychological Corporation 1999) and can be considered a measure of global cognitive functioning. Taken

together, our findings suggest that decreased hippocampal volumes and measures of cognitive capacity and global functioning in association with IR may be harbingers for dementia risk, even while cognitive performance is within the normal range. While the association between hippocampal volume and cognitive ability in pathological aging may predict AD (Devanand et al., 2008), in normal cognitive aging changes are likely to be more subtle (Bennett et al., 2006), as in this sample of highly-educated, middle aged women at risk for AD.

Presence of genetic risk for AD by carriership of APOE- ϵ 4 has been variably ascribed mediating role in the effects of IR on the brain (for example, please see (Craft et al., 2000). In this study, presence of the APOE- ϵ 4 allele did not alter the relationship between IR and hippocampal volume. Consistent with our data, data from den Heijer et al. on the association between IR and hippocampal and amygdalar atrophy in 929 nondemented individuals showed no differentiation with stratification by APOE- ϵ 4 status (den Heijer et al., 2002). Further, the degree of IR has been shown to be similar across APOE polymorphisms (Meigs et al., 2000). On the contrary, the Honolulu Aging Study reported that the co-occurrence of DM2 and APOE- ϵ 4 increased the severity of neuroanatomical abnormalities associated with AD, at least among Japanese-American men (Peila et al., 2002). Among potential explanations for the discrepancy in findings among studies are different populations studied. For example, we studied only women HT users, whereas the Honolulu Aging study included only men.

This study has a number of limitations. As a part of a larger study on brain changes in the postmenopause, it was cross-sectional and as such, precludes inference of causality with respect to potential changes in hippocampal volumes and cognitive decline as a result of IR. Future studies are required to accurately establish the relationship between brain structure and cognitive performance, including cognitive decline, in relation to the metabolic functioning and should include both genders to identify potential gender differences in the relationship of IR with brain structure and cognitive performance. In addition, the effects of hormone therapy should be explored vis-a vis non-users to ascertain the potential interaction between reproductive markers and modifiable (IR) and non-modifiable (APOE- ϵ 4) risk factors for AD.

Despite these limitations, these findings are thought provoking, as they suggest that in cognitively-intact middle aged women, IR is associated with decreased hippocampal volumes and diminished performance on measures of overall global functioning and in selective memory tests. Considering the importance of hippocampal integrity in memory, it is plausible that IR, as an independent metabolic state, may be associated with cognitive deficits and suggest a need for the early identification and treatment of IR in middle-aged persons.

In summary, these results are consistent with a growing body of evidence that links vascular risk factors to cognitive dysfunction in aging and provide additional evidence of the brain mechanisms that may mediate these associations.

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Figure 1. Scatterplot of HOMA-IR and right hippocampal volume (displayed as a ratio of raw right hippocampal volume to total brain volume in cubic centimeters). Please note multiple regression analysis used raw right hippocampal volume as the dependent variable and total brain volume as an independent variable in addition to HOMA-IR). Results showed a significant main effect of HOMA-IR on right hippocampal volume ($t=-2.768$, $p=.008$).

Figure 2. Scatterplot of HOMA-IR and MMSE. Regression results showed a significant association between these two variables ($t=2.773$, $p=.008$)

Table 1

Subject Characteristics (N=50)

	Mean (SD)
Age	57.4 (4.3)
Years of Education	16.0 (1.95)
17-item Hamilton Depression Rating Scale	3.8 (2.9)
Duration of HT Use (years)	10.7 (7.8)
Duration of Endogenous Estrogen Exposure	32.6 (8.2)
BMI	25.5 (3.6)
Fasting Plasma Glucose (mg/dL)	88.1 (10.3)
Fasting Plasma Insulin (mg/dL)	8.6 (3.9)
HOMA-IR	2.0 (1.2)
APOE genotype	$\epsilon 2/\epsilon 3$ –1 (2%)
	$\epsilon 2/\epsilon 4$ –1 (2%)
	$\epsilon 3/\epsilon 3$ –33 (66%)
	$\epsilon 3/\epsilon 4$ –14 (28%)
	$\epsilon 4/\epsilon 4$ –1 (2%)

Table 2**HOMA-IR and Cognitive Performance**

	Mean (SD)	Analysis
ACT Total Score	50.6 (7.1)	t=-2.202, p=.032
ACT Perseverations	3.3 (3.0)	t=2.829, p=.007
ACT Sequencing Errors	1.7 (1.6)	t=2.801, p=.007
BVRT Total Score	6.8 (1.70)	t=-2.494, p=.016
BVRT Errors	4.9 (3.0)	t=2.869, p=.006
BSRT Total Score	68.3 (9.9)	t=-1.552, p=.135
BSRT Perseverations	8.3 (2.4)	t=-0.349, p=.729
BSRT Deletions	3.3 (3.2)	t=0.082, p=.935
MMSE Score	29.1 (0.9)	t=2.773, p=.008
RCFT Immediate Recall	21.9 (5.6)	t=-1.051, p=.298
RCFT Delayed Recall	21.5 (5.4)	t=-0.883, p=.382
WASI-FSIQ	120.5 (10.3)	t=-3.847, p<.001
WASI Matrix Reasoning	61.2 (6.1)	t=-3.953, p<.001
WASI Vocabulary	61.2 (7.7)	t=-4.117, p<.001