Alzheimer's & Dementia 11 (2015) 504-510

Insulin resistance predicts brain amyloid deposition in late middle-aged adults

Auriel A. Willette[a,b,c,†], Sterling C. Johnson[a,b,d,e], Alex C. Birdsill[a,b], Mark A. Sager[b,e], Bradley Christian[f], Laura D. Baker[g], Suzanne Craft[g], Jennifer Oh[a,b], Eric Statz[a,b], Bruce P. Hermann[b,e], Erin M. Jonaitis[e], Rebecca L. Koscik[e], Asenath La Rue[e], Sanjay Asthana[a,b], Barbara B. Bendlin[a,b,*]

[a]*Geriatric Research Education and Clinical Center, Wm. S. Middleton Memorial Veterans Hospital, Madison, WI, USA*
[b]*Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA*
[c]*Laboratory of Neurosciences, National Institute on Aging, Baltimore, MD, USA*
[d]*Waisman Laboratory for Brain Imaging and Behavior, University of Wisconsin-Madison, Madison, WI, USA*
[e]*Wisconsin Alzheimer's Institute, Wisconsin School of Medicine and Public Health, Madison, WI, USA*
[f]*Department of Medical Physics, Wisconsin School of Medicine and Public Health, Madison, WI, USA*
[g]*Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA*

Abstract

Background: Insulin resistance (IR) increases Alzheimer's disease (AD) risk. IR is related to greater amyloid burden post-mortem and increased deposition within areas affected by early AD. No studies have examined if IR is associated with an in vivo index of amyloid in the human brain in late middle-aged participants at risk for AD.

Methods: Asymptomatic, late middle-aged adults (N = 186) from the Wisconsin Registry for Alzheimer's Prevention underwent [C-11]Pittsburgh compound B (PiB) positron emission tomography. The cross-sectional design tested the interaction between insulin resistance and glycemic status on PiB distribution volume ratio in three regions of interest (frontal, parietal, and temporal).

Results: In participants with normoglycemia but not hyperglycemia, higher insulin resistance corresponded to higher PiB uptake in frontal and temporal areas, reflecting increased amyloid deposition.

Conclusions: This is the first human study to demonstrate that insulin resistance may contribute to amyloid deposition in brain regions affected by AD.

Keywords: Insulin resistance; Amyloid; PiB; Alzheimer's disease; Cognitively normal; Prefrontal

1. Background

The etiopathogenesis of Alzheimer's disease (AD) is partly characterized by extracellular β-amyloid (Aβ) aggregation and medial temporal lobe atrophy [1]. Insulin resistance (IR) is associated with brain amyloidosis in rodents and humans [2–6]. IR is characterized by the loss of tissue responsivity to insulin and progressive compensatory peripheral hyperglycemia. Some studies suggest that higher IR is present in AD [1], increases AD risk [7], and is associated with post-mortem Aβ plaques [8]. IR may increase Aβ oligomerization and potentiate brain atrophy via neuroinflammation or other downstream effects [9]. Intranasal insulin therapy has been found to conversely increase plasma Aβ40/42 ratios and improve cognition [10].

No study has examined the direct association between IR and an in vivo marker of amyloid load in AD-sensitive brain areas in late middle-aged participants. Regions of interest (ROIs) include inferior and medial temporal lobe, ventral prefrontal cortex, and posteromedial cortex [6]. Insulin resistance

[†]A.A.W. is now at the National Institute on Aging, but was affiliated with the Wm. S. Middleton Memorial Veterans Hospital and the University of Wisconsin School of Medicine and Public Health when this study was conducted.

*Corresponding author. Tel.: +1-608-265-2483; Fax: +1-608-265-3091.
E-mail address: bbb@medicine.wisc.edu

1552-5260/$ - see front matter
http://dx.doi.org/10.1016/j.jalz.2014.03.011

and type 2 diabetes involve multiple mechanistic pathways, and the effect of IR on neural health may differ depending on whether or not hyperglycemia is present [7,11,12].

In this study, we examined if IR was associated with amyloid binding in three AD-sensitive ROIs based on glycemic status, as found in our previous study on IR and glucose uptake [13]. We hypothesized that higher IR, indexed by the homeostatic model assessment of insulin resistance (HOMA-IR) [14], would predict greater amyloid burden using [C-11] Pittsburgh compound B (PiB) [15] positron emission tomography (PET). On an exploratory basis, we also investigated subregions of these areas to provide greater spatial specificity.

2. Methods

2.1. Participants

One hundred and eighty-six late middle-aged adults from the Wisconsin Registry for Alzheimer's Prevention (WRAP) underwent PiB-PET scanning. Demographics are shown in Table 1. Details about selection criteria, recruitment sources, and other aspects are directly discussed elsewhere [16]. Briefly, this ongoing study examines genetic and biological factors that contribute to the development of dementia-related cognitive decline and neural dysfunction. Participants were classified as either having a positive (FH+) or a negative family history (FH−) of AD. FH+ was defined as having one or both parents with autopsy-confirmed or probable AD as defined by research criteria [17], based on review of medical records and autopsy reports when available. FH− was defined as no formal diagnosis of AD or other significant cognitive decline in either parent, based on information provided by telephone interviews with participants. The inclusion criteria for this study consisted of: normal cognitive function determined by neuropsychological evaluation and consensus meeting similar to Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) recommendations [17], no contraindication for PET or magnetic resonance imaging (MRI) and a subsequently normal MRI scan, no current diagnosis of major psychiatric disease or other major medical conditions (e.g., myocardial infarction, recent history of cancer), and no history of head trauma. The University of Wisconsin Institutional Review Board approved all procedures related to this study. Each participant gave full informed consent before study participation.

Table 1
Participant demographics

N	186
Age in y (mean ± SD)	60.37 ± 5.63
Gender	
Female	129 (69.4%)
Male	57 (30.6%)
Education (mean ± SD)	16.61 ± 2.94
Family history of AD	
Negative	53 (28.5%)
Positive	133 (71.5%)
APOE ε4 status	
Non-*APOE* ε4	114 (61.3%)
APOE ε4	72 (38.7%)
Diabetes status	
Normoglycemia (<100 mg/dl)	135 (72.6%)
At risk/prediabetes (100–125 mg/dl)	43 (23.1%)
Type 2 diabetes (>125 mg/dl)	8 (4.3%)
DBP	74.11 ± 8.98
SBP	124.70 ± 15.19
BMI (mean ± SD)	28.20 ± 5.22
Glucose (mg/dl)	95.01 ± 10.28
Insulin (μU/ml)	9.53 ± 7.60
HOMA-IR (mean ± SD)	2.33 ± 2.19
Total cholesterol (mg/dl)	202.39 ± 34.79
MMSE (mean ± SD)	29.3 ± 0.96
Speed and flexibility (mean ± SD)	0.13 ± 0.86
Working memory (mean ± SD)	0.20 ± 1.11
Verbal learning (mean ± SD)	0.16 ± 0.95
Immediate memory (mean ± SD)	0.15 ± 1.07

Abbreviations: SD, standard deviation; AD, Alzheimer's disease; *APOE* ε4, apolipoprotein ε4 allele; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; HOMA-IR, homeostatic model assessment of insulin resistance; MMSE, Mini-Mental State Examination.

NOTE. The four cognitive factors at the bottom of Table 1 are Z-scores. Number of subjects is listed unless otherwise specified in parentheses.

2.2. Neuropsychological testing

To confirm that participants in this sample were cognitively normal, the Mini-Mental State Examination (MMSE) and neuropsychological factor scores from the full battery [16] were used (see Table 1). Four cognitive domain factors were derived as described previously [18]: immediate memory, verbal learning and memory, working memory, and speed and flexibility. The individual tests which loaded onto the factors were as follows: (1) Rey Auditory Verbal Learning Test [19], Trials 1 and 2 loaded onto Immediate Memory; (2) Rey Auditory Verbal Learning Test [19], Trials 3 to 5 and Delayed Recall Trial loaded onto Verbal Learning & Memory; (3) Wechsler Adult Intelligence Scale – 3rd edition [20], Digit Span, Arithmetic, and Letter-Numbering Sequencing subtests loaded onto Working Memory; and (4) the interference trial from the Stroop Test [21], and Trail Making Test A and B [22] loaded onto Speed & Flexibility. For the MMSE, a cutoff score of 26 was used based on recommended thresholds from the Alzheimer's Disease Neuroimaging Initiative [23]. It is emphasized here that consensus committee meetings in line with NINCDS-ADRDA recommendations [17] were used to confirm if participants were cognitively normal, rather than just the MMSE and other neuropsychological tests.

2.3. APOE *genotype*

Apolipoprotein (*APOE*) genotyping has been described previously [24]. Participants were categorized as "Non-*APOE* ε4" (no ε4 alleles) or "*APOE* ε4" (at least one ε4 allele).