Brief communication

Impaired fasting glucose is associated with increased regional cerebral amyloid

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ABSTRACT

The Alzheimer's disease risk gene apolipoprotein E epsilon 4 (APOE ε4) is associated with increased cerebral amyloid. Although impaired glucose metabolism is linked to Alzheimer's disease risk, the relationship between impaired glycemia and cerebral amyloid is unclear. To investigate the independent effects of APOE ε4 and impaired glycemia on cerebral amyloid, we stratified nondemented subjects (n = 73) into 4 groups: normal glucose, APOE ε4 noncarrier (control [CNT]; n = 31), normal glucose, APOE ε4 carrier (E4 only; n = 14) impaired glycemia, APOE ε4 noncarrier (IG only; n = 18), and impaired glycemia, APOE ε4 carrier (IG+E4; n = 10). Cerebral amyloid differed both globally ($p = 0.023$) and regionally; precuneus ($p = 0.007$), posterior cingulate (PCC; $p = 0.020$), superior parietal cortex (SPC; $p = 0.029$), anterior cingulate ($p = 0.027$), and frontal cortex ($p = 0.018$). Post hoc analyses revealed that E4 only subjects had increased cerebral amyloid versus CNT globally and regionally in the precuneus, PCC, SPC, anterior cingulate, and frontal cortex. In IG only subjects, increased cerebral amyloid compared with CNT was restricted to precuneus, PCC, and SPC. IG+E4 subjects exhibited higher cerebral amyloid only in the precuneus relative to CNT. These results indicate that impaired glycemia and APOE ε4 genotype are independent risk factors for regional cerebral amyloid deposition. However, APOE ε4 and impaired glycemia did not have an additive effect on cerebral amyloid.

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1. Introduction

Type 2 diabetes is a known risk factor for Alzheimer's disease (AD; Morris et al., 2014b), but the relationship between impaired glucose metabolism and cerebral amyloid is not well understood. In cognitively normal subjects, peripheral hyperglycemia is associated with decreased cerebral glucose metabolism (as measured using 2-deoxy-2-(^{18}F)fluoro-D-glucose positron emission tomography [FDG-PET]) in several brain regions, including the precuneus, posterior cingulate, and parietal regions (Burns et al., 2013; Ishibashi et al., 2015a, 2015b; Kawasaki et al., 2008). These areas comprise a set of connections called the default mode network (DMN). They exhibit some of the highest metabolic rates in the brain, (Cavanna and Trimble, 2006; Gusnard et al., 2001), hypometabolism in AD (Bailly et al., 2015; Mosconi, 2005) and are among the first to accumulate amyloid (Hedden et al., 2009).

The most widely recognized risk gene for sporadic AD, apolipoprotein E epsilon 4 (APOE ε4) is consistently associated with

increased cerebral amyloid levels in nondemented subjects (Jansen et al., 2015). However, because of the relationship between peripheral and cerebral metabolism, specifically in DMN regions of interest, it is possible that impaired glycemia is an additional risk factor for accumulation of cerebral amyloid. The effect of glucose on amyloid levels is of particular clinical relevance in the elderly, as cerebral amyloid is a risk factor for AD and 3 quarters of US elderly individuals exhibit prediabetes or diabetes (Cowie et al., 2009). Thus, we stratified our sample into 4 groups to compare the independent and combined effect of each risk factor on cerebral amyloid. This is the first study to investigate the relationship of glucose metabolism, APOE ε4 genotype, and cerebral amyloid in nondemented elderly. We hypothesized that impaired glycemia may be an independent risk factor for elevated cerebral amyloid.

2. Methods

2.1. Approvals and recruitment

This study was approved by the University of Kansas Medical Center's IRB. All participants provided informed consent according to institutional guidelines, and this project was performed in

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accordance with the Declaration of Helsinki. Participants (n = 73) were aged 65 and older, sedentary (Mayer et al., 2008), and free of cognitive impairment (Clinical Dementia Rating of 0). Subjects could not participate if they exhibited insulin-dependent diabetes, uncontrolled hypertension, or recent history of major neuropsychiatric, musculoskeletal, or cardiorespiratory impairment (within 2 years). Cases were further reviewed at a consensus diagnosis conference to ensure normal cognition.

2.2. Metabolic measures

Blood was drawn after an overnight fast. Plasma glucose was quantified (YSI-2300, Yellow Springs Instruments) and subjects classified as normal (NG; FG < 100 mg/dL) or impaired glycemia (IG; FG $\geq$ 100 mg/dL) based on the American Diabetes Association cut-point for impaired fasting glucose. Twelve subjects who met the cut-point for impaired glycemia had a prior diabetes diagnosis, and all diabetic subjects were on diabetic medication. We also quantified additional metabolic biomarkers (Insulin [Genway], amylin [Millipore], and nonesterified fatty acids [Wako Diagnositcs]) in plasma using enzyme-linked immunosorbent assay. Body mass was assessed using a digital scale accurate to 0.1 kg (Seca Platform Scale, model 707). Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated from the product of glucose and insulin divided by 405.

2.3. Subject groups

Individuals were grouped into a control (CNT) group (n = 31) if they had normal glycemia and did not carry the APOE ε4 gene. E4 only (n = 14) subjects had normal glycema and carried at least one copy of APOE ε4. The IG group exhibited impaired glycemia but did not carry APOE ε4, and the combined IG+E4 group were both carriers of APOE ε4 and exhibited impaired glycemia.

2.4. Florbetapir PET

We used Florbetapir PET imaging to measure fibrillar beta-amyloid (Aβ) burden. Participants underwent two 5-minute scans, approximately 50 minutes after intravenous injection of 10 mCi (370 Mbq) of Florbetapir F18 (^{18}F-AV-45). Images were acquired on a GE Discovery ST PET/CT scanner and reconstructed using an iterative reconstruction algorithm, with a 3-mm full-width, half maximum Gaussian filter and were corrected for radiation attenuation and summed. We used Statistical Parametric Mapping 12 (SPM12) software (http://www.fil.ion.ucl.ac.uk/) to process images, manually recentering images and normalizing to Montreal Neurological Institute space using an AV-45−specific PET template. We smoothed the resulting image using a 6-mm full-width, half maximum Gaussian filter. Standard uptake value ratios for 6 a priori defined region of interests (ROIs) were calculated relative to whole cerebellum. The ROI masks were created from the Wake Forest Pick Atlas (Maldjian et al., 2003) and included the anterior cingulate (ACC), posterior cingulate (PCC), precuneus, medial and superior frontal cortex, lateral temporal, occipital, and superior parietal cortex (SPC).

2.5. Statistical analyses

Data are expressed as means ± standard deviation for continuous variables or number and percent for categorical data. Normality was assessed using Shapiro-Wilk tests of normality and non-normally distributed variables were log transformed before univariate analyses. Differences between groups were assessed by 1-way analysis of variance controlling for age and sex. For significant results, post hoc analysis was performed using the least significant difference test.

Categorical data were analyzed by χ^2 analyses. Relationships between continuous variables were analyzed using linear regression. Statistical analyses were performed using SPSS, version 22. Results were considered significant at $p < 0.05$.

3. Results

There were no differences in age, sex, or education or genotype between groups (Table 1). Overall, significant differences in cerebral amyloid between groups were observed both globally ($p = 0.023$) and regionally, in the precuneus ($p = 0.007$), PCC ($p = 0.020$), SPC ($p = 0.029$), ACC ($p = 0.027$), frontal cortex ($p = 0.018$). Post hoc analyses revealed the most widespread increases in E4 only subjects. This group had higher amyloid versus CNT globally ($p = 0.002$) and regionally; precuneus ($p = 0.023$), PCC ($p = 0.015$), SPC ($p = 0.016$), ACC ($p = 0.015$), and frontal cortex ($p = 0.007$). Increased amyloid in the IG only group compared with CNT was restricted to DMN regions; precuneus ($p = 0.013$), PCC ($p = 0.022$), and SPC ($p = 0.030$). The IG+E4 group had the most isolated increase in cerebral amyloid; only differing from CNT in the precuneus ($p = 0.021$). No other intergroup differences aside from those versus the CNT group were significant for any groups. Post hoc findings between groups are summarized in Table 2.

In pooled analyses of all subjects, linear regression did not reveal any relationships between metabolic biomarkers and cerebral amyloid in any region. However, analyses of APOE ε4 carriers and noncarriers separately revealed DMN-specific relationships. In APOE ε4 noncarriers, fasting glucose was positively related to increased cerebral amyloid in the precuneus ($\beta = 0.308$, $p = 0.031$), PCC ($\beta = 0.345$, $p = 0.019$), and SPC ($\beta = 0.320$, $p = 0.029$). In APOE ε4 carriers, no relationships between metabolic biomarkers and cerebral amyloid were observed in any region.

Metabolic differences between the stratified groups were observed for body mass index (BMI; $p = 0.007$) and body weight ($p = 0.029$). Post hoc analyses revealed that the IG+E4 group had higher BMI compared with the CNT ($p = 0.003$) and E4 only ($p = 0.010$) groups, and higher body weight compared with the CNT ($p = 0.018$) and E4 only ($p = 0.008$) groups. The IG only group had higher BMI than the CNT group ($p = 0.017$) and higher body weight compared with the E4 only subjects ($p = 0.032$). Other measures, including fasting insulin, amylin, nonesterified fatty acids, and HOMA-IR were not significantly different between groups.

The number of individuals with a history of diabetes did not differ between the groups with impaired glycemia (IG only and IG+E4). Because all 12 diabetic subjects in this study were taking diabetic medication, (11 metformin, 1 sitagliptin) we reanalyzed the data excluding diabetics. The IG only group still showed increased amyloid versus CNT in the precuneus and SPC but not the PCC, and the effect of increased cerebral amyloid in the precuenus of the E4+IG subjects versus control was also no longer significant. Whether this is due to loss of power or is an effect of diabetic medication warrants further study.

4. Discussion

This is the first study to examine the relationship between impaired glycemia, APOE ε4 genotype, and cerebral amyloid in cognitively-healthy elderly. Individuals with only the risk factor of impaired glycemia (IG only) exhibited higher cerebral amyloid than CNT subjects in 3 highly metabolic brain regions. Even mild increases of fasting glucose in cognitively normal subjects are associated with decreased regional brain glucose metabolism (FDG-PET) in these regions (Ishibashi et al., 2015a, 2015b; Kawasaki et al., 2008) known to show glucose hypometabolism in AD (Minoshima et al., 1997; Mosconi, 2005; Sakamoto et al., 2002).