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Impaired fasting glucose is associated with increased regional cerebral amyloid

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Abstract

The Alzheimer's disease (AD) risk gene apolipoprotein E epsilon 4 (APOE ϵ 4) is associated with increased cerebral amyloid. Although impaired glucose metabolism is linked to AD risk, the relationship between impaired glycemia and cerebral amyloid is unclear. To investigate the independent effects of APOE ϵ 4 and impaired glycemia on cerebral amyloid, we stratified nondemented subjects ($n=73$) into 4 groups: normal glucose, APOE ϵ 4 non-carrier (control (CNT); $n=31$), normal glucose, APOE ϵ 4 carrier (E4 only; $n=14$) impaired glycemia, APOE ϵ 4 non-carrier (IG only; $n=18$) and impaired glycemia, APOE ϵ 4 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 (ACC; $p=0.027$), and frontal cortex ($p=0.018$). Post-hoc analyses revealed that E4 only subjects had increased cerebral amyloid vs. CNT globally and regionally in the precuneus, PCC, SPC, ACC, and frontal cortex. In IG only subjects, increased cerebral amyloid compared to 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 ϵ 4 genotype are independent risk factors for regional cerebral amyloid deposition. However, APOE ϵ 4 and impaired glycemia did not have an additive effect on cerebral amyloid.

Keywords

impaired fasting glucose; insulin; Alzheimer's disease; dementia; metabolism; amyloid; apolipoprotein E

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Introduction

Type 2 Diabetes is a known risk factor for Alzheimer's Disease (AD)(Morris, et al., 2014a) 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 (FDG-PET) in several brain regions, including the precuneus, posterior cingulate, and parietal regions (Burns, et al., 2013, Ishibashi, et al., 2015a, Ishibashi, et al., 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 three quarters of U.S. 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.

Methods

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 accordance with the Declaration of Helsinki. Participants (n=73) were age 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.

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<100mg/dL) or impaired glycemia (IG; FG ≥100mg/dL) based upon 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 non-

esterified fatty acids (NEFA, Wako Diagnostcs)) in plasma using enzyme linked immunosorbent assay. Body mass was assessed using a digital scale accurate to 0.1kg (Seca Platform Scale, model 707). HOMA-IR was calculated from the product of glucose and insulin divided by 405.

Subject Groups

Individuals were grouped into a control group (CNT; n=31) if they had normal glycemia and did not carry the APOE ϵ 4 gene. E4 only (n=14) subjects had normal glycemia and carried at least one copy of APOE ϵ 4. The IG group exhibited impaired glycemia but did not carry APOE ϵ 4, and the combined IG+E4 group were both carriers of APOE ϵ 4 and exhibited impaired glycemia.

Florbetapir PET

We used Florbetapir PET imaging to measure fibrillar beta-amyloid (A β) burden. Participants underwent two 5-min scans, approximately 50min after intravenous injection of 10mCi (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 3mm full-width, half maximum Gaussian filter and were corrected for radiation attenuation and summed. We used SPM 12 (<http://www.fil.ion.ucl.ac.uk/>) to process images, manually recentering images and normalizing to Montreal Neurological Institute space using a AV-45 specific PET template. We smoothed the resulting image using a 6mm full-width, half maximum Gaussian filter. Standard uptake value ratios (SUVRs) for 6 *a priori* defined 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).

Statistical analyses

Data are expressed as means $\pm$ SD 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 prior to univariate analyses. Differences between groups were assessed by one-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 chi-squared analyses. Relationships between continuous variables were analyzed using linear regression. Statistical analyses were performed using SPSS version 22. Results were considered significant at $p < 0.05$.

Results

There were no differences in age, sex, or education or genotype between groups. 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 vs. 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 to 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 inter-group differences aside from those vs. 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 $\epsilon 4$ carriers and noncarriers separately revealed DMN-specific relationships. In APOE $\epsilon 4$ 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 $\epsilon 4$ 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 ($p=0.007$) and body weight ($p=0.029$). Post-hoc analyses revealed that the IG+E4 group had higher BMI compared to the CNT ($p=0.003$) and E4 only ($p=0.010$) groups, and higher body weight compared to 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 to the E4 only subjects ($p=0.032$). Other measures, including fasting insulin, amylin, non-esterified 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 re-analyzed the data excluding diabetics. The IG only group still showed increased amyloid vs. CNT in the precuneus and SPC, but not the PCC, and the effect of increased cerebral amyloid in the precuneus of the E4+IG subjects vs. control was also no longer significant. Whether this is due to loss of power or is an effect of diabetic medication warrants further study.

Discussion

This is the first study to examine the relationship between impaired glycemia, APOE $\epsilon 4$ 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 three 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, Ishibashi, et al., 2015b, Kawasaki, et al., 2008) known to show glucose hypometabolism in AD (Minoshima, et al., 1997, Mosconi, 2005, Sakamoto, et al., 2002). Interestingly, APOE $\epsilon 4$ carriers with impaired glycemia (IG +E4) exhibited more isolated increases in cerebral amyloid, while APOE $\epsilon 4$ carriers with normal glucose levels exhibited the most widespread increases in cerebral amyloid.

Prior studies of peripheral metabolism and cerebral amyloid are mixed. In late middle aged adults with normal glucose, greater insulin resistance (HOMA-IR) is associated with greater

amyloid burden in two broad ROI's (frontal and temporal)(Willette, et al., 2015). A much smaller study of the relationship between diabetes diagnosis and cerebral amyloid in 4 ROI's (anterior cingulate, frontal cortex, parietal cortex, and precuneus) showed no relationship (Moran, et al., 2015). An additional study found that insulin resistance was not predictive of cerebral amyloid in elderly subjects, and found no relationship between glucose and postmortem AD pathology (Thambisetty, et al., 2013). However, subjects were grouped in tertiles (not an established cut-point) based upon either fasting or 120 minute post-oral glucose tolerance test values. Impaired fasting glucose and impaired glucose tolerance are different states of insulin resistance that do not necessarily define the same subjects or state of metabolic impairment (Nathan, et al., 2007). Studies using glucose tolerance testing may differ compared to studies examining fasting measures; thus, inconsistent findings may due to differing methodology for defining impaired glucose or insulin resistance.

Our study used a clinically accepted, readily available cut-point for to analyze this relationship and yields interesting insight on the potentially separate effects of impaired glycemia and APOE ϵ 4 on cerebral amyloid pathology. Elevated insulin often precedes high glucose by compensating for mild insulin resistance (Prentki and Nolan, 2006) and hyperglycemia develops with the onset of beta-cell dysfunction and loss of compensation. Here, fasting insulin was not significantly different across groups. This is noteworthy because both glucose (Macauley, et al., 2015) and insulin (Gasparini, et al., 2001, Kulstad, et al., 2006, Reger, et al., 2008) affect amyloid production and trafficking, but may involve different pathways or having different magnitudes of effect on A β (reviewed in (Sato and Morishita, 2015).

Impaired glycemia is associated with disease progression in mild cognitive impairment (Morris, et al., 2014b, Velayudhan, et al., 2010). This study extends these findings by showing that prior to cognitive impairment, impaired glycemia is associated with increased cerebral amyloid in DMN regions of subjects not at genetic (APOE-mediated) AD risk. It is postulated that because neuronal depolarization, repolarization and protein trafficking all involve high energy demand, bioenergetic failure may play a key role in AD (Pathak, et al., 2013, Swerdlow, et al., 2010). Peripheral hyperglycemia is associated with hypometabolism in the brain, (Ishibashi, et al., 2015a, Ishibashi, et al., 2015b, Kawasaki, et al., 2008) and animal studies suggest that deficits in cellular energy metabolism affect the processing and transport of A β *in vitro* and *in vivo*. (Chao, et al., 2016, Kong, et al., 2015, Macauley, et al., 2015) and excess A β may in turn exacerbate hypometabolism (Tarczyluk, et al., 2015).

An additional consideration of this study includes diabetes medication use. Laboratory studies have shown that the first-line diabetes medication metformin both increases (Chen, et al., 2009, Picone, et al., 2015) and decreases (Hettich, et al., 2014) BACE1 expression, which could affect cerebral amyloid levels. It is worth noting that autopsy studies have failed to show that diabetes diagnosis is associated with increased amyloid pathology, (Alafuzoff, et al., 2009, Arvanitakis, et al., 2006) although most studies have assessed global markers of neuropathology, and our findings of increased amyloid pathology in the groups with impaired glycemia were regional in nature. In fact, the E4 only group was the only group to show significantly higher global cerebral amyloid. Additional well-powered studies are

needed to evaluate the potential effect of diabetes and diabetic medication on regional cerebral amyloid in humans.

An important limitation of this study is the small sample size. While A β loads seemed similar between IG only and IG+E4 groups, particularly in DMN regions, this effect was significant in IG only subjects in the precuneus, PCC, and SPC, but only in the precuneus in the IG+E4 group, possibly due to lack of power. In addition, our measures of glucose metabolism are limited to peripheral, rather than cerebral measures. However, this adds to the current literature by indicating that peripheral hyperglycemia, which is very easy to measure with noninvasive measures, is related to cerebral amyloid deposition in subjects not at genetic AD risk in highly metabolic brain regions. In conclusion, this study shows regional differences in cerebral amyloid deposition due to both genotype and glycemic status in cognitively-healthy elderly. This is important as it suggests that regional amyloid deposition tracks with impairments in glucose metabolism prior to cognitive impairment in elderly individuals not at genetic AD risk, and further substantiates the building evidence that impaired glucose metabolism is a significant risk factor for the development of cognitive impairment in particular cohorts.

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Highlights

- Hyperglycemia is associated with increased default mode network amyloid in E4 negatives
- Fasting glucose correlates with cerebral amyloid in the precuneus, PCC and SPC
- Hyperglycemia and APOE E4 genotype together do not exacerbate cerebral amyloid

Table 1
Demographic, metabolic, physiologic, and neuroimaging outcomes

		CNT (n=31)	E4 only (n=14)	IG only (n=18)	IG+E4 (n=10)	p- value
Demograp	Age (y)	73.0 [6.3]	72.0 [5.5]	74.2 [6.1]	71.1 [4.5]	0.558
	Sex, n [% male]	14 [45.2%]	1 [7.1%]	9 [50.0%]	4 [40.0%]	0.060
	Education (yrs)	16.6 [2.8]	15.9 [3.5]	16.2 [2.9]	15.3 [1.8]	0.515
	Diabetes history, n [%]	0 [0.0%]	0 [0.0%]	7 [39%]	5 [50%]	<0.01*
Metabolic	Glucose (mg/dL)	88.8 [7.6]	84.0 [9.6]	107.3 [19.1]	118.3 [11.8]	<0.01*
	Insulin (μU/mL)	7.01 [7.5]	6.69 [5.6]	15.67 [19.0]	10.3 [8.1]	0.361
	Amylin (pM) [‡]	13.03 [27.7]	12.5 [14.2]	16.9 [21.6]	10.3 [11.0]	0.221
	NEFAs (mmol/L) [‡]	0.40 [0.21]	0.40 [0.47]	0.64 [0.80]	0.61 [0.78]	0.093
Physiologic	HOMA-IR	1.55 [1.72]	1.40 [1.16]	4.28 [5.71]	2.95 [2.36]	0.085
	Systolic BP (mmHg)	127.8 [13.6]	131.8 [16.8]	130.9 [18.3]	132.0 [15.5]	0.755
	Diastolic BP (mmHg)	75.1 [7.6]	76.1 [9.5]	73.1 [8.0]	78.4 [9.2]	0.469
	Waist:Hip ratio	0.88 [0.08]	0.87 [0.06]	0.93 [0.07]	0.89 [0.09]	0.075
Neuroimaging	BMI	27.2 [4.3]	27.3 [4.3]	30.1 [4.0]	31.7 [2.6]	0.007*
	Weight (kg)	76.1 [15.6]	73.5 [12.8]	88.1 [19.5]	90.1 [12.3]	0.029*
	Precuneus	1.15 [0.14]	1.30 [0.22]	1.30 [0.27]	1.32 [0.23]	0.007*
	Posterior cingulate (PCC)	1.16 [0.11]	1.28 [0.15]	1.26 [0.17]	1.25 [0.15]	0.020*
	Superior parietal cortex (SPC)	1.07 [0.10]	1.18 [0.17]	1.16 [0.18]	1.15 [0.16]	0.029*
	Anterior cingulate (ACC)	1.20 [0.15]	1.35 [0.24]	1.28 [0.22]	1.32 [0.19]	0.027*
	Medial and superior frontal	1.02 [0.13]	1.17 [0.20]	1.08 [0.19]	1.11 [0.18]	0.018*
	Lateral temporal	1.08 [0.06]	1.14 [0.08]	1.11 [0.09]	1.10 [0.11]	0.179
	Occipital	1.05 [0.06]	1.11 [0.10]	1.08 [0.11]	1.08 [0.10]	0.258
	Global cortical	1.03 [0.06]	1.12 [0.09]	1.08 [0.10]	1.07 [0.09]	0.023*

All values given are means and SD. All analyses were controlled for sex and age.

[‡] Available on a subset of subjects (n=69).

SUVR: standard uptake value ratio.
* p<0.05

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Table 2
Post-hoc comparisons of cerebral amyloid between groups

Differences were only significant vs. the control group and varied from widespread regions (E4 only) to primarily DMN-related regions (IG only) and finally only to the precuneus (IG+E4 group).

Region	E4	IG	IG+E4
Precuneus	↑ vs. CNT	↑ vs. CNT	↑ vs. CNT
Posterior cingulate (PCC)	↑ vs. CNT	↑ vs. CNT	
Superior parietal cortex (SPC)	↑ vs. CNT	↑ vs. CNT	
Anterior cingulate (ACC)	↑ vs. CNT		
Medial and superior frontal	↑ vs. CNT		
Global cortical	↑ vs. CNT		