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The relationship between fasting serum glucose and cerebral glucose metabolism in late-life depression and normal aging

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ABSTRACT

Evidence exists for late-life depression (LLD) as both a prodrome of and risk factor for Alzheimer's disease (AD). The underlying neurobiological mechanisms are poorly understood. Impaired peripheral glucose metabolism may explain the association between depression and AD given the connection between type 2 diabetes mellitus with both depression and AD. Positron emission tomography (PET) measures of cerebral glucose metabolism are sensitive to detecting changes in neural circuitry in LLD and AD. Fasting serum glucose (FSG) in non-diabetic young (YC; $n=20$) and elderly controls (EC; $n=12$) and LLD patients ($n=16$) was correlated with PET scans of cerebral glucose metabolism on a voxel-wise basis. The negative correlations were more extensive in EC versus YC and in LLD patients versus EC. Increased FSG correlated with decreased cerebral glucose metabolism in LLD patients to a greater extent than in EC in heteromodal association cortices involved in mood symptoms and cognitive deficits observed in LLD and dementia. Negative correlations in YC were observed in sensory and motor regions. Understanding the neurobiological consequences of diabetes and associated conditions will have substantial public health significance given that this is a modifiable risk factor for which prevention strategies could have an important impact on lowering dementia risk.

1. Introduction

Late-life depression (LLD) has a substantial public health impact given its association with serious disability, completed suicide, and mortality in the medically ill elderly (Henriksson et al., 1995; Alexopoulos et al., 1996; Conwell et al., 1996). Cognitive impairment is a common feature of LLD and often persists after mood symptom remission (Alexopoulos et al., 1993a, 1993b; Bhalla et al., 2006). Furthermore, substantial evidence suggests LLD is both a risk factor for and a prodrome of dementia. A meta-analysis estimated that depression doubles the risk of subsequent Alzheimer's disease (AD) (Ownby et al., 2006). However, the mechanisms linking LLD to cognitive impairment and dementia are poorly understood. Ultimately, understanding these mechanisms will allow for the identification of individuals with LLD at increased risk for subsequent cognitive decline and identification of treatment targets to prevent or delay transition to dementia.

Abnormal glucose metabolism may represent a mechanistic link between LLD and dementia (Rasgon and Jarvik, 2004). Individuals with type 2 diabetes mellitus (DM) have elevated rates of AD and vascular dementia (Schmidt et al., 1992; Pasquier et al., 2006). Depression approximately doubles the risk for future development of type 2 DM (Eaton et al., 1996). Though hyperglycemia defines DM, hyperglycemia is not an immediate feature of insulin resistance, which is the underlying pathophysiologic abnormality of type 2 DM. When an individual develops insulin resistance, the pancreas initially increases insulin production to maintain euglycemia. Ultimately, insulin resistance overwhelms the compensatory insulin response and hyperglycemia develops. Insulin resistance is a continuous process. However, diabetes and "pre-diabetes" (impaired glucose tolerance and impaired fasting glucose) are diagnosed only by measured hyperglycemia (American Diabetes Association, 2013). Of note, some depressed individuals manifest insulin resistance (Nathan et al., 1981; Menna-Perper et al., 1984; Winokur et al., 1988; Okamura et al., 2000; Hennings et al., 2010), which improves with depression

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treatment (Mueller et al., 1969; Nathan et al., 1981; Okamura et al., 2000; Weber-Hamann et al., 2008; Hennings et al., 2010).

Positron emission tomography (PET) studies of cerebral glucose metabolism demonstrate sensitivity to detecting changes in neural circuitry associated with depression and dementia, as well as in individuals at genetic risk for AD (Reiman et al., 1996; Mayberg et al., 2000; Smith et al., 2009a, 2009b; Diaconescu et al., 2011). In cognitively normal adults with "pre-diabetes" or early type 2 DM, Baker et al. showed that greater insulin resistance was associated with an AD-like pattern of reduced cerebral glucose metabolism (Baker et al., 2011). In healthy subjects (age range 47–68 years), Burns et al. reported a correlation between higher fasting serum glucose (FSG) and lower cerebral glucose metabolism in regions affected in AD. This correlation was stronger in individuals carrying the APOE 4 allele, an AD risk factor (Burns et al., 2013). Thus, even in cognitively normal subjects, higher FSG may be associated with vulnerability to AD-like changes in cerebral glucose metabolism.

The present analyses correlated FSG with cerebral glucose metabolism in non-diabetic young controls (YC) and elderly controls (EC) as well as non-diabetic LLD patients. The hypotheses tested were as follows: (1) Increased FSG will correlate with decreased cerebral glucose metabolism in LLD patients. The negative correlations will be observed in frontal and parietal heteromodal association cortices, which are implicated in mood and cognitive symptoms in LLD, and also demonstrate decreased cerebral glucose metabolism and neuropathology in AD (neurofibrillary tangles and amyloid plaques). These areas include the anterior cingulate, middle frontal, posterior cingulate, precuneus, and fusiform gyri (Arnold et al., 1991; Langbaum et al., 2009; Smith et al., 2009b; Diaconescu et al., 2011). (2) The negative correlations will be greater in the LLD patients than in the EC group in frontal and parietal association cortices. (3) The negative correlations will be greater in the EC group compared with the YC group in frontal and parietal association cortices.

2. Methods

2.1. Subject screening and selection

LLD patients, EC subjects, and YC subjects underwent psychiatric evaluation including a structured clinical interview (First et al., 1995), laboratory testing (including complete blood count, blood chemistry including screening glucose level, thyroid function tests, and toxicology screening), and brain magnetic resonance (MR) imaging scan (GE 1.5 T Magnetom Vision) before the PET scans. The subjects were enrolled in a study to evaluate the acute effects of the antidepressant citalopram on cerebral glucose metabolism. The data for the baseline (placebo) PET scans in the LLD patients and controls have been published previously (Goldberg et al., 2004; Smith et al., 2009a, 2009b).

The sample included 16 older adults who met DSM-IV criteria for current major depressive episode as well as 20 YC and 12 EC subjects who did not meet DSM-IV criteria for current or past Axis I psychiatric disorders (as shown in Table 1). None of the participants had a prior diagnosis of diabetes mellitus or screening laboratory values consistent with diabetes mellitus (i.e. random blood glucose $\geq$ 200 mg/dl, fasting blood glucose $\geq$ 126 mg/dl). Exclusion criteria were as follows: past or current neurological disorder, other Axis I psychiatric disorder (including substance abuse), lack of medical stability (including uncontrolled hypertension), and use of a centrally acting medication or supplement within the past 2 weeks (including beta blockers, benzodiazepines, antihistamines, and cold medications). All subjects were scanned on 2 consecutive days after an infusion of either placebo (250 ml of saline; scan 1) or citalopram (40 mg of the drug diluted in 250 ml of saline; scan 2) over 60 min (Smith et al., 2009a). For the present study, only the PET scans following placebo infusions were included in the analysis, before the citalopram was administered.

Thirteen of the LLD patients had never been treated with psychotropic medications (including antidepressants and antipsychotics). Of the remaining three patients, two took sertraline before study entry (stopped 6 months to 2 years before enrollment). The third patient took nortriptyline for 2 years up until 2 weeks before the PET scan (at which time the plasma nortriptyline concentrations were undetectable). None of the patients had taken citalopram previously. After a complete study description to potential participants, written informed consent was obtained according to procedures established by the Institutional Review Board and the Radiation Safety Committee of the North Shore-Long Island Jewish Health System.

2.2. PET imaging procedures

PET scans were performed using a GE Advance Tomograph in the Center for Neurosciences, Feinstein Institute for Medical Research, as described previously (Smith et al., 2009a, 2009b; Diaconescu et al., 2011). All PET studies began at the same time of day (10 AM). Subjects were instructed not to eat after midnight the evening before the scans. Upon arrival at the PET facility, subjects received one intravenous catheter in the left arm for radiotracer infusion and a second catheter in the right arm for sampling of glucose and citalopram levels. Five mCi of [^{18}F]-2-deoxy-2-fluoro-D-glucose ([^{18}F]-FDG) was injected as an intravenous bolus. The FSG determined at this time was used for the correlation analyses. During the [^{18}F]-FDG uptake interval, the subjects sat in a darkened, quiet room with eyes open and ears unoccluded. At 25 min after radiotracer injection, subjects were positioned in the GE Advance Tomograph. A 10-min transmission scan and a 5-min two-dimensional emission scan were acquired first to perform photon attenuation correction. A three-dimensional emission scan began 40 min after radiotracer injection and lasted for 10 min. At the end of the scan, subjects were debriefed as to their perceptions of the study.

2.3. Data and image analysis

Glucose metabolic rates were calculated (in ml/100 g/min) on a voxel-wise basis according to validated methods (Takikawa et al., 1993). PET data processing was performed on the quantitative glucose metabolism images using the Statistical Parametric Mapping program (SPM5, Institute of Neurology, London). This is a data-driven analytic approach that performs statistical tests on each voxel in the image. In summary, for each subject, all PET scans were realigned using a generated mean image (the placebo scan 1 was used for the analyses in this article). The PET scans were normalized to the SPM5 PET template in Montreal Neurological Institute (MNI) space and then smoothed with an isotropic Gaussian kernel (full width at half maximum 8 mm for all directions). The glucose metabolic rates were normalized by scaling to a common mean value across all scans, after establishing that the global means did not differ significantly between and within groups at each time point ($p > 0.05$). The data were normalized to a global mean because of the greater test-retest variability for absolute compared with relative glucose metabolism observed in numerous studies (e.g., Bartlett et al., 1988). Voxel-wise correlations between FSG and cerebral glucose metabolism were performed for the EC subjects, EC subjects, and LLD patients separately using the one-sample *t*-test option with FSG as a covariate in SPM5. Then, the correlations were compared between groups with the two-sample *t*-test option with FSG as a covariate. Representative design matrices for the two analytic methods are provided as supplemental material. The two comparisons performed were the YC versus the EC and the EC versus LLD. To control for multiple comparisons, both probability level and cluster size thresholds were used. The comparisons were considered significant at a *t* threshold greater than 2.98 ($z > 2.58$, $p < 0.005$; uncorrected for multiple independent comparisons) and at a predetermined cluster size greater than 100 voxels. The comparisons that were also significant at the at the uncorrected cluster level are indicated ($p < 0.05$). The results were not significant when corrected for multiple comparisons. The significance level reported was similar to recent studies that showed an association between FSG and glucose metabolism (Burns et al., 2013).

3. Results

3.1. Subject characteristics

The demographic characteristics and FSG at the time of PET scanning for YC, EC and LLD subjects appear in Table 1. The YC subjects were significantly younger than the EC subjects and the LLD patients ($p < 0.01$), but the EC subjects and the LLD patients did not differ significantly in age ($p > 0.1$). The three groups did not differ significantly in years of education, FSG or body-mass index (BMI) ($p > 0.1$). The EC subjects and the LLD patients did not differ significantly in global cognitive function ($p > 0.1$) as measured by the Mini-Mental Status Examination (MMSE) and the Dementia Rating Scale (DRS) (Folstein et al., 1975; Mattis, 1976).

Correlations of FSG with age, BMI, depressive symptoms, cognition (California Verbal Learning Test [CVLT], and verbal fluency) were not significant within groups. Thus, these variables were not used in the statistical analyses. Gender was correlated