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Association between insulin resistance and cognition in patients with depressive disorders: Exploratory analyses into age-specific effects

Tonita E. Wroolie, Heather A. Kenna, Manpreet K. Singh, Natalie L. Rasgon*

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, USA

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ABSTRACT

The current preliminary cross sectional study sought to examine the effects of insulin resistance (IR) and body mass index (BMI) on cognitive performance in adult patients with a history depression, currently not in an acute Major Depressive Episode (MDD). As an exploratory post hoc investigation, special consideration was given to adults <45 years and ≥45 years old.

Subjects included men and women ages 19-71 ($N = 39$) with a history of a non-psychotic, non-melancholic MDD. All subjects underwent an insulin suppression test to determine Steady-State Plasma Glucose (SSPG), a battery of neuropsychological tests, and measurement of BMI. Multiple linear regressions were conducted to determine whether there were differential effects of direct (SSPG) and indirect (BMI) measures on cognition in the whole sample and within dichotomized age groups (<45 and ≥45 years).

Preliminary results showed that in the sample as a whole, SSPG was not associated with worse performance on any cognitive variables, while higher BMI was associated with worse dominant hand fine motor skills. Within age groups, differential effects on cognition were found in relation to SSPG and BMI. Higher SSPG was associated with worse cognitive flexibility in the group <45 years, whereas higher BMI was associated with worse estimate of global intelligence in the group ≥45 years.

The potential negative impact of IR in younger adults with depression raises concerns regarding the long-term impact on cognition and risk for Alzheimer's disease in undiagnosed younger adults with IR and depression. These negative consequences may not be seen with indirect measures of IR in younger adult populations. Overweight and obesity in older adults with a history of depression appear to have further negative impacts on cognition similar to deficits seen in patients with diabetes.

ClinicalTrials.gov Identifier: Clinical Trial NCT01106313

1. Introduction

Clinical depression is now the second leading cause of global disability with the highest rates of incidence affecting working-aged adults, and women more so than men. Major depressive disorder (MDD) and type 2 diabetes (DM2) share numerous pathophysiological characteristics that suggest bidirectional links between the central nervous system (CNS) and endocrine homeostasis. Patients with DM2 have a high incidence of depression (Ali et al., 2006), and reciprocally, patients with depression are at increased risk of developing DM2 (Golden et al., 2004) possibly due to poor lifestyle habits (Yu et al., 2014). Insulin resistance (IR), a subclinical state that often precedes the development of DM2, is often accompanied by depressive symptomatology (Golden et al., 2004; Viscogliosi et al., 2013) and patients with mood disorders have biomarkers suggestive of high IR (Gold et al., 2005; Soczynska et al., 2011). In the general population, it is estimated that approximately 1/3 of healthy, non-obese adults are insulin resistant, even after controlling for body mass index (BMI) (Reaven, 2011). It is also estimated that as many as 50% of individuals with DM2 remain undiagnosed (American Diabetes Association, 2006).

Both MDD and DM2 are characterized by a loss of neuronal integrity over time in the limbic area leading, most notably to hippocampal atrophy (Bremner et al., 2000). Not surprisingly, deficits in hippocampal-mediated functions related to attention, and executive functioning accompany both disorders (Rasgon and Jarvik, 2004). These same cognitive abilities appear to improve

* Corresponding author. Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5723, USA. Tel.: +1 650 724 6689; fax: +1 650 724 3144.
E-mail address: nrasgon@stanford.edu (N.L. Rasgon).

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with glycemic control in patients with DM2 (Awad et al., 2004). In contrast, cognitive deficits observed in patients with MDD remain even after remission of depressive symptoms (Paelecke-Habermann et al., 2005; Weiland-Fiedler et al., 2004), possibly due to underlying IR (Rasgon et al., 2004; Rasgon and Kenna, 2005). Furthermore, IR in patients with depression often remains even after remission of depressive symptoms (Gold et al., 2005).

Clear evidence demonstrates cognitive impairment in patients with IR (Awad et al., 2002) as well as in patients with DM2 (Awad et al., 2004). Furthermore, IR has been described in patients with mild cognitive impairment and Alzheimer's disease (Craft, 2006). Obesity in midlife is also associated with increased IR and risk of vascular and Alzheimer's dementias (Kivipelto et al., 2005). The persistence of cognitive deficits in patients with remitted depression suggests underlying, untreated brain pathology that over time may lead to disease processes such as Alzheimer's disease (AD). The present study sought to examine whether a bidirectional link, independent of depression, exists between insulin sensitivity and performance on selective cognitive tasks. Additionally, we sought to explore whether cognitive deficits in patients with depression were due in part to underlying untreated impairment in insulin sensitivity which itself may have contributed to the onset of depression (Rasgon and Jarvik, 2004).

The main aim of this preliminary study was to explore the relations among a direct quantitative measure of IR (steady-state plasma glucose) and a surrogate marker of IR (BMI) with cognitive performance in euthymic patients with a history of MDD. We hypothesized that a greater degree of IR as well as higher BMI would be associated with worse performance on a priori selected cognitive measures. IR and diabetes have been shown to be associated with declines in executive functioning, attention, fine motor, and processing speed (Espeland et al., 2011; Pavlik et al., 2013) as well as with increased cerebral atrophy (de Bresser et al., 2010) and a decline on global cognitive measures (Marioni et al., 2010). Our study hypothesized that these areas of cognition would be most vulnerable to the effects of IR and chose measures that would provide assessment of these abilities. Furthermore, given that increasing age is a major risk factor for increasing IR and cognitive decline, exploratory post hoc analyses gave specific consideration to younger adults (<45 years of age) versus older adults (≥45 years of age, i.e., middle aged and above).

2. Research design and methods

The Stanford University Institutional Review Board approved the study. Participants were recruited through advertisements in the community and referrals from medical and psychiatry outpatient clinics. All participants provided informed consent prior to study enrollment. Men and women ages 19–71 ($N = 45$) with a history of non-psychotic, non-melancholic major depressive disorder (MDD), currently not in an acute depressive episode were included. Baseline assessment consisted of insulin suppression test and a full battery of neuropsychological tests. Participants met the following inclusion criteria: self-reported cognitive complaints, non-diabetic as evidenced by screening of fasting plasma glucose (<100 mg/dL), adequate visual and auditory acuity to allow neuropsychological testing, stable regime of psychotropic medications for at least 6 weeks prior to study procedures, and intact cognition as evidenced by Mini Mental Status Examination (MMSE) scores of ≥28. Subjects in an acute episode of depression were excluded. Other exclusion criteria included pregnancy or breastfeeding (women), a personal history of Type 1 or Type II diabetes, unstable cardiovascular disease or other major medical condition, history of myocardial infarction within the previous year, significant cerebrovascular disease, as evidenced by neurological examination, uncontrolled hypertension (systolic blood pressure >170 or diastolic blood pressure >100), current drug or alcohol abuse, history of neurological disorder (e.g. multiple sclerosis, stroke), significant cognitive deficits upon testing (evidence of mild cognitive impairment or dementia), or current use of psychotropic medications that have potential metabolic confounds (see (Deuschle, 2013) for a review) or use of any medication that may significantly affect psychometric or insulin testing.

2.1. Clinical assessments

At baseline screening, subjects underwent a physical and neurological examination and were asked about personal and family medical history, and current prescription and over-the-counter medications, including vitamins and herbal products. Subjects were asked about first-degree relatives with DM2, as well as other major metabolic disorders (e.g. thyroid), and dementia or psychiatric disorders. Height and weight were assessed for calculation of body mass index. Electrocardiogram was conducted as needed to establish patient safety for the Insulin Suppression Test.

The psychiatric examination utilized the Structured Clinical Interview for DSM-IV (SCID; (First et al., 1997)) and the 21-item Hamilton Depression Rating Scale (HDRS-21; (Hamilton, 1980)). The SCID was administered in its entirety at the eligibility-screening visit to confirm Axis I diagnosis of Major Depressive Disorder. The clinician-administered HDRS-21 assessed current depressive symptoms and participants with a cut-off score of ≤20 (normal or mild symptoms) were evaluated.

2.1.1. Steady-State Plasma Glucose (SSPG)

Insulin resistance was quantified by a modification (Pei et al., 1994) of the insulin suppression test as described and validated by Reaven and colleagues (Greenfield et al., 1981). This direct measure of insulin resistance is on par with the hyperinsulinemia euglycemic clamp, considered the “gold standard” of insulin resistance measurement, while being less patient-invasive and costly. Briefly, after an overnight fast, octreotide was administered at 0.27 μg/m2/min to suppress endogenous insulin secretion. Simultaneously, insulin and glucose were infused at 32 mU/m2/min and 267 mg/m2/min, respectively. Blood samples for glucose and insulin levels were taken every half hour until 150 min into the study, and then every 10 min until 180 min had elapsed. Insulin concentrations typically plateau by 60 min, whereas glucose concentrations plateau after 120 min. The four values obtained from 150 to 180 min were averaged and considered to represent the steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations achieved during the infusion. Since SSPI concentrations are comparable in all individuals, both qualitatively and quantitatively, and the glucose infusion rate identical, the magnitude of the resultant SSPG concentration provides an accurate estimate of how effective insulin is in disposal of a glucose load, i.e., the higher the SSPG, the more insulin resistant the person. It should be noted that quantification of insulin action with the insulin suppression test and the euglycemic, hyperinsulinemic clamp are highly correlated, with r-value $= -0.87$, and $p < .001$ (Greenfield et al., 1981).

2.1.2. Cognitive testing

The neuropsychological battery consisted of selected tasks from the Benton Visual Retention Test (BVRT) (Benton, 1974), Delis-Kaplan Executive Functioning System (D-KEFS) (Delis et al., 2001), Purdue Pegboard (Tiffin and Asher, 1948), Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III; (Corporation, 1997)), and