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Glucose-6-phosphate dehydrogenase activity in bipolar disorder and schizophrenia: Relationship to mitochondrial impairment

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) is the first and rate-limiting enzyme of the pentose phosphate pathway that is essential to maintaining cellular redox balance. G6PD is especially plentiful in brain, and its deficiency has been linked to mood and psychotic disorders. We measured G6PD activity spectrophotometrically in four groups of 15 parietal somatosensory association cortex [Brodmann area (BA) 7] tissue samples (N = 60) from individuals with bipolar disorder (BPD); nonpsychotic unipolar major depression (UPD); schizophrenia (SCZ), and controls without psychiatric illness (CON). We report for the first time brain G6PD activity levels in these disorders. G6PD activity did not differ by brain group. In BPD and SCZ brains, however, it correlated significantly and inversely with percent of hexokinase 1 (HK1) in the tissue homogenate mitochondrial fraction as determined previously in another set of tissue samples obtained from the same brains and brain region. The correlation in SCZ brains lost statistical significance after controlling for brain pH. This finding indicates a positive relationship in BPD brains between G6PD activity and HK1 mitochondrial detachment, an indicator of mitochondrial impairment associated with increased mitochondrial generation of reactive oxygen species. We speculate that this relationship could be evidence that G6PD activity is proportionate to and may be a compensatory response to oxidative stress in the BA7 region of BPD brains. Future research should focus on clarifying the relationships among G6PD activity, markers of oxidative stress, brain pH, and evidence of mitochondrial impairment, particularly HK1 mitochondrial detachment, in brains of individuals with G6PD deficiency, BPD and SCZ.

1. Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is a cytosolic enzyme that is the first and rate-limiting enzyme of the pentose phosphate pathway that oxidizes glucose-6-phosphate (G6P) to produce the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) (Kletzien et al., 1994). NADPH is a major cellular reducing equivalent, which is essential to reductive biosynthesis and maintenance of the cellular redox state in part through the reduction of glutathione (GSH), a key antioxidant. The expression and activity of G6PD are increased in response to oxidative stress (Ursini et al., 1997).

The human brain is particularly rich in G6PD activity with the highest activity level per unit protein of any organ (Battistuzzi et al., 1985). A link between G6PD deficiency, which is the most common enzyme deficiency (Luzzatto et al., 2014; Nkhoma et al., 2009), and mood or psychotic disorders has been investigated for more than fifty years with mixed results (Berrettini et al., 1990; Bocchetta, 2003; Del Zompo et al., 1984; Dern et al., 1963; Mendlewicz et al., 1980; Monsivais et al., 2016; Nasr, 1976; Raj et al., 2014; Singh et al., 2012). To our knowledge, reports so far are limited to G6PD activity as measured in blood or erythrocytes with no reports of G6PD activity measured in the CNS of individuals with mood or psychotic disorders.

We undertook the present study to examine G6PD activity in postmortem brain tissue and determine its relationship to our previous finding of detachment of hexokinase 1 (HK1) from the outer mitochondrial membrane (OMM) in postmortem parietal cortex [Brodmann area (BA) 7] tissue of individuals with nonpsychotic unipolar major depression (UPD), bipolar disorder (BPD) and schizophrenia (SCHZ) compared to tissue from controls without psychiatric illness (CON) (Regenold et al., 2012). HK1 is an initial and rate-limiting enzyme of glycolysis (Wilson, 2003). HK1 mitochondrial attachment is a critical feature of brain energy metabolism, because it greatly enhances HK1 enzyme activity and couples cytosolic glycolysis to mitochondrial oxidative phosphorylation, through which the cell produces

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most of its adenosine triphosphate (ATP) (BeltrandelRio and Wilson, 1992). HK1 mitochondrial attachment is also important to the survival of neurons and other cells through prevention of oxidative damage (da-Silva et al., 2004; Liemburg-Apers et al., 2015). G6P, which is the product of HK1 and the substrate of G6PD, is a key modulator of HK1 attachment to the OMM. Increasing cytosolic concentration of G6P in the vicinity of the OMM detaches HK1 from the OMM inducing feedback inhibition of HK1 activity (Wilson, 2003). Decreased activity of G6PD would therefore increase the cytosolic concentration of G6P, thereby decreasing HK1 OMM attachment. However, HK1 OMM detachment impairs mitochondrial function resulting in the mitochondrial generation of reactive oxygen species (ROS) and cellular oxidative stress, which could trigger a compensatory increase in G6PD activity.

2. Material and methods

2.1. Postmortem brain samples

This study was reviewed by the University of Maryland, Baltimore Institutional Review Board and determined not to be human subjects research. We used postmortem, fresh-frozen, parietal somatosensory association (BA7) cortex tissue from the Stanley Neuropathological Consortium (Rockville, MD, USA). We studied brains from individuals with BPD (n = 15), UPD (n = 15), SCZ (n = 15), CON (n = 15). Demographic, clinical, and brain-related information was not revealed to the research team until completion of all experiments and submission of data, ensuring blinded data collection. Samples were sent frozen on dry ice and stored at −70 to −80 °C until use. Samples were matched for age, race, gender, brain pH and postmortem interval (PMI), and side of brain, with no significant differences among groups on these variables. The mean (± standard deviation) values for age, pH, and postmortem interval (PMI) were 45.4 ± 11.2 years, 6.2 ± 0.23, and 29.4 ± 13.4 h, respectively. Sixty percent of individuals were male, and racial composition was: Caucasian (n = 56), African American (n = 2), and Asian (n = 2). Thirty-seven of the 45 individuals with psychiatric illness had been taking CNS medications at the time of death, and eight had been free of CNS medications for at least several months prior to death. Demographic and clinical characteristics of individuals and methods of brain tissue processing have been published elsewhere in detail (Torrey et al., 2000).

2.2. Tissue preparation

Tissue samples were thawed on ice immediately before preparation. Thawed tissue was dissected under microscope to separate gray matter from white matter and blood vessels. Gray matter was weighed and homogenized using a hand held Dounce homogenizer (Kontes Glass, Vineland, NJ) in ice-cold isolation medium (pH = 7.43) containing Tris 50 mM and protease inhibitors (Sigma-Aldrich, St. Louis, MO, USA). Homogenate was sonicated ten times with 1 s bursts at a medium intensity (Branson 1510, Sigma Aldrich, St. Louis, MO, USA), and then centrifuged at 4 °C at 15,000 g for 10 min. Supernatant from each sample was aliquoted and frozen at −70 to −80 °C.

2.3. Glucose-6-phosphate dehydrogenase assay

Total protein concentration for each sample was determined in duplicate using the BCA Protein Assay Kit (Thermo Scientific Pierce, Rockford, IL, USA) according to manufacturer's instructions. G6PD activity was assayed in duplicate using the Glucose-6-Phosphate Dehydrogenase Kit (Sigma Aldrich, St. Louis, MO, USA) and 96-well plates according to manufacturer's instructions. Activity was detected spectrophotometrically according to the amount of NADH produced through G6PD oxidation of G6P by measuring absorbance at λ = 450 nm with an OPTIMA multimodal plate reader (BMG LABTECH, Inc., Cary, NC) at 37 °C. Absorbances were recorded every 5 min for 1 h. G6PDH activity was calculated by measuring the amount of NADH produced in a 30-min period, between 10 min and 40 min after the reaction was begun. G6PD activity was expressed as nmol NADH produced per minute per mg total protein (nmol NADH/min/mg protein).

2.4. Statistics

Continuous variables were assessed for normal distribution by the Shapiro-Wilk test. If data were not distributed normally, we either $\log_{10}$ transformed data or used nonparametric statistics including the median and interquartile range (IQR), Kruskal-Wallis test, Mann-Whitney *U* test, and Spearman's rho (ρ) to analyze group distributions, group differences and correlations, respectively. We used correlations and dichotomous group comparisons to assess relationships between demographic, clinical, or neuropathologic (e.g. PMI) variables and G6PD activity. Categorical variables were analyzed using Pearson's chi square (χ^2) test. All tests were two-tailed, and alpha was set at p = 0.05. We used SPSS version 12.0 (SPSS, Inc., Chicago, IL, USA) for analyses.

3. Results

The cause of death distribution by brain group is shown in Table 1. For the G6PD assay, average intra-assay and inter-assay coefficients of variation were 1.4%, and 3.7%, respectively. G6PD activity did not differ significantly (χ^2 = 1.04, df = 3, p = 0.791) across the four brain groups [median (IQR)]: BPD [5.72 (2.56)]; UPD [5.21 (3.21)]; SCHZ, [6.29 (3.59)], and HC [5.41 (2.86)] nmol NADH/min/mg protein (Fig. 1). G6PD activity also did not differ significantly (p ≥ 0.267) by side of brain, gender, race, diabetes mellitus diagnosis, death by suicide, smoking, use of CNS medication at the time of death, or specific use of lithium, antidepressant, mood stabilizer, benzodiazepine, or antipsychotic medication at the time of death. G6PD activity did not correlate significantly (p ≥ 0.147) with brain weight, number of days a brain was frozen, PMI, age, age of onset of psychiatric illness, duration of psychiatric illness, severity of substance or alcohol abuse, or extent of antipsychotic medication use expressed as lifetime fluphenazine equivalents. G6PD activity did, however, correlate significantly with brain pH (ρ = −0.546, p < 0.001). Analysis of covariance with $\log_{10}$G6PD activity as the dependent variable and pH as covariate did not reveal a significant difference among brain groups (F = 0.165, df = 3, 55, p = 0.919).

To assess the relationship of G6PD activity to HK1 mitochondrial detachment, we examined correlations between G6PD activity and percent of HK1 in the tissue homogenate mitochondrial fraction, which represents the HK1 attached to the OMM rather than free in the cytosol,

Table 1
Cause of death distribution by brain group.

Cause of death	BPD	UPD	SCZ	CON	Total
Cardiac	4	9	4	6	23
Suicide: Overdose	1	2	3	1	7
Pulmonary Embolus	1	0	1	3	5
Suicide: Jumped	3	0	0	2	5
Motor Vehicle Accident	0	1	1	1	3
Pneumonia	2	0	0	1	3
Suicide: Carbon Monoxide	2	1	0	0	3
Suicide: Hanged	2	0	1	0	3
Acute Alcohol Intoxication	0	1	1	0	2
Accidental Drowning	0	0	0	1	1
Malnutrition and Dehydration	0	0	1	0	1
Pulmonary Disease	0	0	1	0	1
Suicide: Gunshot	0	0	1	0	1
Subdural Hematoma	0	1	0	0	1
Suicide: Immolation	0	0	1	0	1

Abbreviations: BPD = bipolar disorder; UPD = unipolar major depression, nonpsychotic; SCZ = Schizophrenia; CON = controls without psychiatric illness (CON).

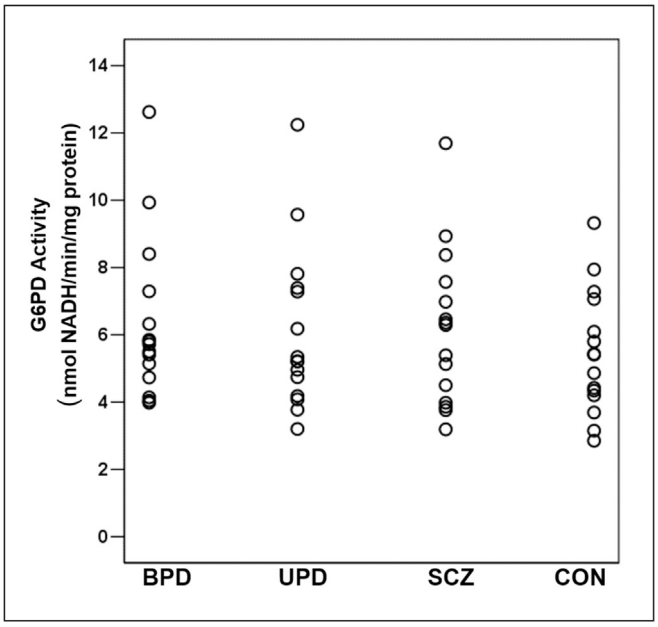

Fig. 1. Scatter plot of G6PD activity in parietal somatosensory association cortex (BA7) tissue by postmortem brain group (n = 15 per group).

as determined previously by quantitative western blot in another set of tissue samples obtained from the same brains and brain region (Regenold et al., 2012). Significant negative correlations were observed in the entire set of samples ($\rho = -0.447$, $p < 0.001$) and separately in BPD ($\rho = -0.889$, $p < 0.001$) and SCZ ($\rho = -0.532$, $p = 0.041$) groups, but not in UPD ($\rho = -0.127$, $p = 0.652$) or CON ($\rho = -0.114$, $p = 0.685$) groups (Fig. 2). Partial correlation controlling for pH was significant in the BPD group ($\rho = -0.556$, $df = 12$, $p = 0.039$), but not in the entire set ($\rho = -0.194$, $df = 57$, $p = 0.140$) nor in the SCZ ($\rho = -0.389$, $df = 12$, $p = 0.170$); UPD ($\rho = 0.066$, $df = 12$, $p = 0.882$), and CON ($\rho = -0.083$, $df = 12$, $p = 0.777$) groups.

4. Discussion

To our knowledge, this is the first report of brain G6PD activity in individuals with UPD, BPD and SCZ. Our principal finding is that G6PD activity correlated significantly and inversely, while controlling for brain pH, with the percent of HK1 attached to the OMM in postmortem parietal somatosensory association cortex (BA7) tissue from BPD brains, but not from SCZ, UPD or CON brain groups. This relationship indicates that G6PD activity is highest when cellular HK1 is most detached from the OMM, indicating a positive relationship between G6PD activity and evidence of mitochondrial impairment in BPD brain. The relationship was strongest in the BPD group, and lost significance in the SCZ group when controlling for brain pH. As attachment of HK1 to the OMM prevents oxidative damage by reducing mitochondrial ROS (da-Silva et al., 2004), we speculate that this relationship could be evidence that G6PD activity is proportionate to and may be a compensatory response to the level of cellular oxidative stress in the BA7 region of BPD brains. G6PD activity in BPD brains does not, however, exceed that of CON brains and therefore may be insufficient to maintain a normal redox balance under elevated oxidative stress. Similarly, the lack of an adequate G6PD compensatory response to oxidative stress in individuals with G6PD deficiency could explain their vulnerability to mood and psychotic disorders as others have hypothesized (Monsivais et al., 2016).

Our finding of an association between G6PD activity and HK1 mitochondrial detachment is consistent with the increasing evidence of the interdependent roles of mitochondrial impairment and oxidative stress in the pathophysiology of BPD and SCHZ (Andreazza et al., 2010, 2013; Bitanihirwe and Woo, 2011; Kim et al., 2017; Prabakaran et al., 2004). The cellular redox balance is highly dependent on mitochondrial function. Oxidative phosphorylation at the electron transport chain of the mitochondrion is a major source of ATP as well as ROS in the cell. Mitochondrial dysfunction, evidenced here by HK1 OMM detachment, is linked to enhanced glycolytic activity and inefficient oxidative phosphorylation resulting in an increased amount of ROSs created per molecule of glucose oxidized (Andreazza et al., 2010; Kim et al., 2017; Liemburg-Apers et al., 2015).

This study had significant limitations. Firstly, the sample number is small, which limited the power of our analyses, particularly when assessing for potential confounds such as brain pH and medication use. Although the negative correlation in the SCZ group between GPD activity and percent of HK1 in the mitochondrial fraction lost statistical significance when controlling for pH, it is important to consider that use of partial correlations on small sample sizes has been reported to increase type II error (false negative) by 29–85% (Knudson and Lindsey, 2014). Secondly, the study lacked a marker of oxidative stress to test our hypothesis that the relationship between G6PD activity and HK1 mitochondrial detachment is mediated through oxidative stress. Finally, in any postmortem study there is the potential confound of peri- and postmortem factors. G6PD activity did not correlate significantly with PMI; however, it did correlate inversely and significantly with brain pH. A negative correlation between G6PD activity and brain pH could reflect an increase in G6PD activity in response to a prolonged agonal or hypoxic peri-mortem state (Li et al., 2004; Vawter et al., 2006). However, there is evidence from a meta-analysis of postmortem brain studies and an animal model study that lower brain pH may be a shared endophenotype of BPD and SCZ rather than an artifact of peri-mortem state (Hagihara et al., 2018). Moreover, some research suggests that pH is reduced in the living CNS in these disorders, possibly due to mitochondrial dysfunction with brain lactate accumulation (Dager et al., 2004; Dogan et al., 2018; Regenold et al., 2009).

Future research should focus on clarifying the relationships among G6PD activity, markers of oxidative stress, brain pH, and evidence of mitochondrial impairment, particularly HK1 mitochondrial detachment, in brains of individuals with G6PD deficiency, BPD and SCZ. Biomarkers characterizing these pathophysiologic relationships in individual patients could eventually be used in treatment trials to assess the biologic effects of pro-mitochondrial or antioxidant treatments and to individualize therapy for these disorders (Dogan et al., 2018; Kim et al., 2007; Regenold et al., 2009). Reports of supplementation with N-acetyl cysteine, a precursor to the antioxidant glutathione, decreasing symptoms by 40% in an individual with G6PD deficiency-associated psychosis and improving cognitive performance in individuals with SCZ and BPD-related psychosis are encouraging (Monsivais et al., 2016; Rapado-Castro et al., 2017).

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Author disclosure

The authors declare no conflict of interest.

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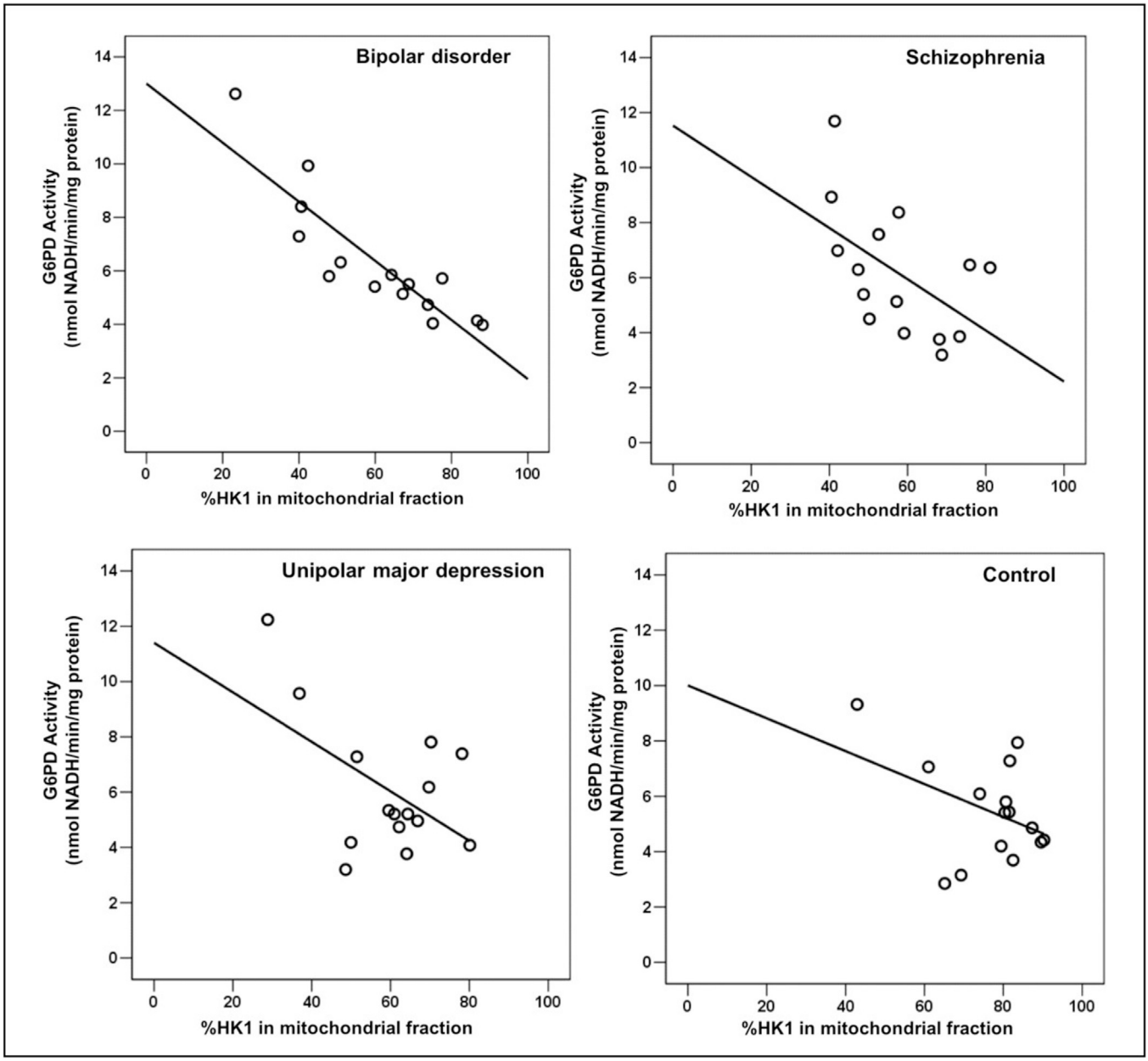

Fig. 2. Scatter plots of the relationship of G6PD activity to percent (%) hexokinase 1 (HK1) in tissue homogenate mitochondrial fraction of parietal somatosensory association cortex (BA7) tissue by postmortem brain group (n = 15 per group).

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