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Peripheral and central glucose utilizations modulated by mitochondrial DNA 10398A in bipolar disorder

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Summary Bipolar disorder (BD) is highly heritable and associated with dysregulation of brain glucose utilizations (GU). The mitochondrial DNA (mtDNA) 10398A polymorphism, as a reported BD risk factor, leads to deficient glycolytic energy production by affecting mitochondrial matrix pH and intracellular calcium levels. However, whether mtDNA-10398A has functional effects on the brain and how our body responds remain elusive. We compared peripheral and central glucose-utilizing patterns between mtDNA A10398G polymorphisms in BD and their unaffected siblings (BDsib). Since siblings carry identical mtDNA, we hypothesized that certain characteristics co-segregate in BD families. We recruited twenty-seven pairs of non-diabetic BD patients and their BDsib and 30 well-matched healthy control subjects (HC). The following were investigated: mtDNA, fasting plasma glucose/insulin, cognitive functions including Montreal Cognitive Assessment (MoCA), and brain GU at rest. Insulin resistance was rechecked in sixty-one subjects (19-BD, 18-BDsibib, and 24-HC) six months later. We found that BD-pairs (BD + BDsib) carried more mtDNA-10398A and had higher fasting glucose, even after controlling for many

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covariates. BD-pairs had abnormally lower dorso-prefrontal-GU and higher cerebellar-GU, but only BD demonstrated lower medio-prefrontal-GU and MoCA. Subjects carrying mtDNA-10398A had significantly lower prefrontal-GU (FWE-corrected $p < 0.05$). An abnormal inverse pattern of insulin-GU and insulin-MoCA correlation was found in BD-pairs. The insulin-MoCA correlation was particularly prominent in those carrying mtDNA-10398A. mtDNA-10398A predicted insulin resistance 6 months later. In conclusion, mtDNA-10398A was associated with impaired prefrontal-GU. An up-regulation of glucose utilizations was found in BD-pairs, probably compensating for mtDNA-10398A-related energy loss.

1. Introduction

Bipolar disorder (BD) is a highly heritable disorder (McGuffin et al., 2003), characterized by mood swings between extremely high-energy (mania) and low-energy (depression) states. A wide range of drugs available for the treatment of BD (e.g., valproate, lithium, and atypical antipsychotics) are able to treat mood symptoms (Bai et al., 2013), leaving some other symptoms (e.g., cognitive dysfunction) untreated. Such insufficient therapeutic effects of the available medications imply that the underlying pathophysiology of BD remains obscure and new therapeutic target is warranted.

Several lines of evidence indicate that mitochondrial dysfunction plays a critical role in the pathophysiology of BD (Kato, 2006; de Sousa et al., 2014). For example, studies investigating in vivo brain chemistry by magnetic resonance spectroscopy (MRS) revealed that BD involves impaired oxidative phosphorylation, altered phospholipid metabolism, increased intracellular pH, a resultant shift toward glycolytic energy production, and a decrease in total cerebral energy production (Stork and Renshaw, 2005). Mitochondria are the most important organelles in most eukaryotic cells that regulate cellular metabolism and convert glucose to ATP energy which organisms need. Glucose is the main energy source for the human brain. Impaired brain glucose utilizations have been reported in functional studies of positron emission tomography (PET) investigating BD patients, such as hypo-utilizations in the prefrontal cortex (Buchsbaum et al., 1986; Baxter et al., 1989). The observed hypofrontality was left untreated even during patients' euthymic state and also accountable for the cognitive deficits in remission (Li et al., 2012). Impaired cognitive function (e.g., executive dysfunction) has been also reported in the unaffected relatives of BD patients (Arts et al., 2008; Balanza-Martinez et al., 2008; Bora et al., 2009). However, whether the mitochondrial dysfunction hypothesis of BD could also explain the altered cerebral glucose utilizations (e.g., impaired prefrontal utilization) remains elusive.

Another piece of evidence supporting BD as a heritable disorder is from mitochondrial genetic studies. For example, mitochondria DNA (mtDNA) 10398A polymorphism is one of the reported mtDNA polymorphisms associated with BD (Kato and Kato, 2000). BD patients carrying mtDNA-10398A seems to respond better to lithium (Washizuka et al., 2003). Given the polymorphism plays a role in glycolytic energy production by affecting mitochondrial matrix pH and intracellular calcium levels, the resulting mitochondrial dysfunction would lead to an ineffective production of ATP energy from glucose and might have an impact on human brains. However, whether mtDNA-10398A has functional effects on brain glucose utilizations (GU) and long-term glucose homeostasis remains elusive.

Therefore, in the present study, we investigated mtDNA A10398G polymorphism, fasting plasma glucose and insulin, cognitive functions, and brain GU as measured by resting ^{18}F-FDG PET, and their relationships among three groups of subjects without a history of diabetes mellitus: (1) BD patients, (2) unaffected siblings of the BD patients (BDsib), and (3) healthy control subjects (HC). We hypothesized that, in response to insufficient glycolytic energy production, some compensatory glucose-utilizing characteristics might be observed and co-segregate in BD families.

Since siblings carry identical mtDNA, we thus investigated central and peripheral glucose-utilizing patterns in BD and BDsib and the effects from mtDNA-10398 polymorphisms were compared. To further investigate whether long-term mitochondrial dysfunction might affect the glucose homeostasis, homeostasis model assessment for insulin resistance (HOMA-IR) (Matthews et al., 1985) was tested at baseline and re-tested six months later between subjects with and without the mtDNA-10398A.

2. Methods and materials

2.1. Participants

Eighty-four subjects were recruited, including twenty-seven pairs of stable BD subtype I patients and their unaffected BDsib (age differences < 5 years in the BD pairs) and 30 age-, gender-, and ethnicity-matched HC (Table 1). Subtype I of BD patients were selected mainly due to its high heritability (Gershon et al., 1982), and the diagnoses were established by structured history-taking and administration of the Mini International Neuropsychiatric Interview (MINI) based on the Fourth Edition of the Diagnostic and Statistical Manual system criteria. The recruited BDsib and HC were all free of axis I disorders, and all subjects were free of major medical and neurological illness, a lifetime alcohol or substance abuse history. HC subjects with a family history of an axis I disorder were also excluded. To reduce potential confounding effects from medications, all recruited patients were either clinically stable off medications or had stop taking medications for at least five days before the enrollment. Furthermore, sixty-one subjects (19-BD, 18-BDsib, and 24-HC) had fasting plasma sugar and insulin rechecked six months