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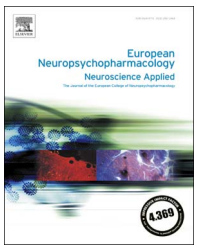

Second generation antipsychotic-induced mitochondrial alterations: Implications for increased risk of metabolic syndrome in patients with schizophrenia

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Abstract
Metabolic syndrome (MetS) is seen more frequently in persons with schizophrenia than in the general population, and these metabolic abnormalities are further aggravated by second generation antipsychotic (SGA) drugs. Although the underlying mechanisms responsible for the increased prevalence of MetS among patients under SGA treatment are not well understood, alterations in mitochondria function have been implicated. We performed a comprehensive evaluation of the role of mitochondrial dysfunction in the pathophysiology of drug-induced MetS in schizophrenia. We found a downregulation in genes encoding subunits of the electron transport chain complexes (ETC), enzyme activity, and mitochondrial dynamics in peripheral blood cells from patients at high-risk for MetS. Additionally, we evaluated several markers of energy metabolism in lymphoblastoid cell lines from patients with schizophrenia and controls following exposure to antipsychotics. We found that the high-risk drugs clozapine and olanzapine induced a general down-regulation of genes involved in the ETC, as well as decreased activities of the corresponding enzymes, ATP levels and a significant decrease in all the functional parameters of mitochondrial oxygen consumption in cells from patients and controls. We also observed that the medium-risk SGA quetiapine decreased oxygen consumption

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and respiratory control ratio in controls and patients. Additionally, clozapine and olanzapine induced a downregulation of Drp1 and Mfn2 both in terms of mRNA and protein levels. Together, these data suggest that an intrinsic defect in multiple components of oxidative metabolism may contribute to the increased prevalence of MetS in patients under treatment with SGAs known to cause risk for MetS.

1. Introduction

Schizophrenia is a chronic, severe, and disabling mental disorder characterized by deficits in thought processes, perceptions, and emotional responsiveness. Schizophrenia has a lifetime prevalence of 1.1% in adults in the United States, and it is estimated that 21 million people are affected worldwide (WHO). Atypical or second-generation antipsychotics (SGAs) are medications that are commonly used to treat this disorder. However, treatment with SGAs may increase the risk of metabolic syndrome (MetS), weight gain and cardiovascular complications (Basu et al., 2004; Hasnain et al., 2010). The prevalence of MetS in patients with schizophrenia is higher than in the general population (Heiskanen et al., 2003; McEvoy et al., 2005). Studies estimate the prevalence of MetS as ranging from 14.7% to 68% in patients with schizophrenia who are under drug treatment, with about a three-fold greater risk of developing MetS than the general population in both clinical and community samples (Boke et al., 2008; Cohn et al., 2004; Kato et al., 2004).

The underlying mechanism for the increased prevalence of MetS among patients under SGA treatment is not well understood. A number of explanations have been proposed, including drug actions on lipid and carbohydrate metabolism, the tendency to accumulate intra-abdominal adiposity and fat, alterations of the hypothalamic pituitary-adrenal axis, poor blood glucose control, and mitochondrial dysfunction (Basu et al., 2004; Burkhardt et al., 1993; Ji et al., 2009; Rosmond, 2002). In regards to the latter hypothesis, evidence that mitochondria are a target of atypical antipsychotics arises from several studies. Brains of rats exposed to these drugs show changes in mitochondrial functions, oxidative phosphorylation (OXPHOS) and mRNA expression of mitochondrial proteins (Hroudova and Fisar, 2010; Ji et al., 2009; Streck et al., 2007). Davey et al. (1998) showed that a small antipsychotic-induced loss in complex I activity was sufficient to decrease ATP synthesis and mitochondrial respiration by approximately 35%. Moreover, antipsychotic medications induce ultrastructural changes in mitochondria and production of reactive oxygen species (ROS) (Abdel-Wahab and Metwally, 2014; Contreras-Shannon et al., 2013; Fehsel et al., 2005). A study using isolated lymphoblasts showed that clozapine increased the oxidative damage of a limited group of proteins related to mitochondrial function (Baig et al., 2010).

We have previously found that SGAs that differ in their risk for inducing MetS are also associated with differences in alterations of energy metabolism pathways, where clozapine and olanzapine are associated with the greatest disturbances (Paredes et al., 2014). However, the specific molecular mechanisms by which different types of SGAs alter mitochondrial functions are not understood. Therefore, in this study we performed a comprehensive examination of the effects of SGAs on mitochondria function in peripheral blood cells from schizophrenia patients compared to controls. Because mechanisms of mitochondria dysfunction are also attributed to the development of obesity, insulin resistance, and other metabolic complications, understanding how SGAs increases risk for MetS may lead to a better understanding of the mechanisms underlying metabolic disorders in the population at large.

2. Experimental procedures

2.1. Subjects

This study was carried out in accordance with the principles of the Declaration of Helsinki with approval from the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and written informed consent was obtained from all research participants. Sixty patients with schizophrenia and 20 healthy controls (HC) were recruited from local community mental health centers, and control participants were recruited through advertisements in the community. Patients and HC were matched for ethnicity, age and socioeconomic status. All patients met the DSM-IV-TR criteria for schizophrenia by the SCID for the DSM-IV. Each patient was on the same antipsychotic treatment for at least three months prior to enrolling in the study and blood sample collection. Patients were stratified based on the risk for antipsychotic-induced MetS, determined by the type of SGA being prescribed at the time of enrollment (Paredes et al., 2014). When more than one type of SGA was being taken, the risk level for that patient was based on the highest risk SGA. SGAs have been classified based to the risk to induce weight gain and body mass index (BMI) increase, which are considered, according to the National Cholesterol Education Program (NCEP) (2001) and the International Diabetes Federation (IDF), indicators of MetS (Alberti et al., 2006). According to studies, clozapine and olanzapine impose the highest metabolic side effects (high risk), followed by quetiapine and risperidone (medium risk), while ziprasidone and aripiprazole are less likely to cause metabolic side effects (low risk) (Bou Khalil, 2012; Newcomer, 2007; Tschoner et al., 2009). Based on this, the following three risk levels for developing MetS were established: high (clozapine, olanzapine; $N = 22$), medium (quetiapine, risperidone; $N = 27$), or low (ziprasidone, aripiprazole; $N = 11$) risk. HC were screened for DSM-IV axis I disorders using the SCID non-patient version. HC who had a history of diabetes and/or dyslipidemia, or who had current or past axis I DSM-IV psychiatric disorders, or first-degree relatives with any axis I psychiatric disorder were excluded from the study. Therefore, none of the subjects were being treated for type II diabetes or were under insulin treatment. Fasting blood was drawn by venipuncture from each subject in heparin collection tubes, followed by isolation of peripheral blood mononuclear cells

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