

Research Article

Increased Susceptibility to Ethylmercury-Induced Mitochondrial Dysfunction in a Subset of Autism Lymphoblastoid Cell Lines

Shannon Rose, Rebecca Wynne, Richard E. Frye, Stepan Melnyk, and S. Jill James

Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital Research Institute, 13 Children's Way, Slot 512-41B, Little Rock, AR 72202, USA

Correspondence should be addressed to Shannon Rose; srose@uams.edu

Received 18 September 2014; Revised 12 December 2014; Accepted 13 December 2014

Academic Editor: Maria Teresa Colomina

Copyright © 2015 Shannon Rose et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The association of autism spectrum disorders with oxidative stress, redox imbalance, and mitochondrial dysfunction has become increasingly recognized. In this study, extracellular flux analysis was used to compare mitochondrial respiration in lymphoblastoid cell lines (LCLs) from individuals with autism and unaffected controls exposed to ethylmercury, an environmental toxin known to deplete glutathione and induce oxidative stress and mitochondrial dysfunction. We also tested whether pretreating the autism LCLs with N-acetyl cysteine (NAC) to increase glutathione concentrations conferred protection from ethylmercury. Examination of 16 autism/control LCL pairs revealed that a subgroup (31%) of autism LCLs exhibited a greater reduction in ATP-linked respiration, maximal respiratory capacity, and reserve capacity when exposed to ethylmercury, compared to control LCLs. These respiratory parameters were significantly elevated at baseline in the ethylmercury-sensitive autism subgroup as compared to control LCLs. NAC pretreatment of the sensitive subgroup reduced (normalized) baseline respiratory parameters and blunted the exaggerated ethylmercury-induced reserve capacity depletion. These findings suggest that the epidemiological link between environmental mercury exposure and an increased risk of developing autism may be mediated through mitochondrial dysfunction and support the notion that a subset of individuals with autism may be vulnerable to environmental influences with detrimental effects on development through mitochondrial dysfunction.

1. Introduction

Autism spectrum disorders (ASD) are defined as a heterogeneous group of neurodevelopmental disorders characterized by impairments in communication and social interactions along with restrictive and repetitive behaviors [1]. The incidence of ASD in the United States is currently estimated to be 1 in 68 individuals, and it continues to rise [2]. While the etiology of ASD remains unknown, multiple interacting genetic and environmental factors are thought to contribute to the development of ASD. In addition to behavioral impairments, recent studies indicate that many children with ASD also exhibit impairments in energy production and redox homeostasis [3–5].

Multiple studies have demonstrated the presence of glutathione-mediated redox imbalance and oxidative stress in individuals with ASD [5–11]. Our group has consistently reported decreased concentrations of glutathione (GSH) and several of its metabolic precursors as well as increased

oxidized glutathione disulfide (GSSG) and a decreased glutathione redox ratio (GSH/GSSG) in plasma, immune cells, and postmortem brain from children with ASD [4, 5, 11–13]. Oxidative stress and damage have been documented in blood and brain of individuals with ASD including reports of decreased levels and activities of antioxidant enzymes and elevated levels of oxidized lipids, proteins, and DNA [4, 7, 8, 11, 14, 15]. In primary lymphocytes and in lymphoblastoid cell lines (LCLs) derived from children with autistic disorder (AD), we have found that the production of reactive oxygen species (ROS) is elevated as compared to controls [12, 13, 16]. The imbalance between glutathione-mediated antioxidant capacity and ROS production in autism LCLs may cause these cells to be more susceptible to oxidative stress and damage from any exogenous sources of ROS as compared to control LCLs.

Recent evidence indicates that the incidence of mitochondrial dysfunction in ASD may be very high, affecting up to 30% or more of children with ASD [17]. While the etiology