Increased Receptor for Advanced Glycation End Products (RAGE) in Children with Autism

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Abstract

Receptor for advanced glycation end products (RAGE) is an immunoglobulin superfamily receptor that binds to HMGB1. High mobility group box 1 (HMGB1) proteins are diverse nuclear proteins that function as proinflammatory cytokines. In this study we measured RAGE in autistic children, with and without GI disease. In this study, we found RAGE significantly increased in an autistic group, particularly those with GI disease. This suggests that a HMGB1/RAGE pathway may be associated with inflammation seen in many individuals with autism.

Keywords: Receptor for Advanced Glycation End Products (RAGE); High Mobility Group Box 1 (HMGB1); Autism

Introduction

Receptor for advanced glycation end products (RAGE) is an immunoglobulin superfamily receptor that binds to HMGB1 [1] and HMGB1-RAGE signaling is associated with several cancers [2,3]. So, HMGB1 secretion is considered to be associated with anti-cancer inflammation which occurs during chemotherapy [4]. As a result, HMGB1 may be a biomarker of inflammation, as well as a marker associated with the prognosis of certain tumor progression.

High mobility group box 1 (HMGB1) proteins are nuclear proteins with extensive functional diversity. These proteins were first purified from cell nuclei in the 1970s [5]. The HMGB1 gene produces a protein product that contains two 80-amino acid DNA-binding domains (A-box and B-box) and a negatively charged C-terminus [6]. Intra-nuclear HMGB1 is a chromatin structural protein, while extracellular HMGB1 acts as a proinflammatory cytokine [7,8]. HMGB1 is also multi-functional, which could be the reason it is associated with the etiology of Alzheimer's disease [9] and arthritis [10].

There is evidence that a RAGE dependent HMGB1 pathway helps promote intestinal inflammation [11]. We previously reported significantly higher levels of HMBG1 in an autistic group [12]. This study measured RAGE in autistic children with and without GI disease.

Methods

Subjects

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Plasma RAGE was measured in 27 (20 male mean age 10.6 years) autistic children and 22 age and neurotypical controls (17 male mean age 13.2 years). Subject plasmas were gotten from the Autism Genetic Resource Exchange (AGRE).

This study was approved by the IRB of the Health Research Institute.

Plasma

All plasma was received frozen and immediately placed at -70°C before Immunoassay analysis.

Immuno-array assays

Immuno-array assays were performed by RayBiotech, Inc, Peachtree Corners, GA. 30092, as previously described [18].

Statistics

Unpaired t-test and odds ratios with 95% confidence intervals was used for statistical analysis.

Results

Plasma RAGE was measured in 27 (20 male mean age 10.6 years) autistic children and 22 age and gender similar neurotypical controls (17 male mean age 13.2 years) using immuno-arrays. We found that Individuals with autism had significantly higher RAGE (393 +/- 136 pg/µl) when compared to RAGE in controls (312 +/- 68) (p = 0.03) (Figure 1).

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We also found that autistic individuals with GI disease had significantly higher RAGE (504 +/- 151 pg/µl) than autistic individuals without GI disease (358 +/- 56 pg/µl) (p = 0.04) (Figure 2).

**Figure 2:** Autistic individuals with GI disease had significantly higher RAGE (504 +/- 151 pg/µl) than autistic individuals without GI disease (358 +/- 56 pg/µl) (p = 0.04).

**Discussion**

High mobility group box-1 (HMGB1) is a prominent mediator of inflammatory diseases. It is a nuclear protein that initiates inflammation, binds to IL-1 and lipopolysaccharides (LPS), and works with a Toll-like receptor (TLR) 4-mediated pro-inflammatory response [13]. HMGB1 is actively released from activated monocytes and macrophages after the proinflammatory stimulation by cytokines. Regulation of HMGB1 secretion is dependent on processes such as phosphorylation by calcium-dependent protein kinase C [14], as well as acetylation and methylation [15]. HMGB1 and TLR4 have been associated with seizures in experimental animals [16,17].

**Conclusion**

The data presented here shows that RAGE is significantly higher in autistic individuals, and those autistic individuals with GI disease have significantly higher RAGE than those that do not have GI disease. We suggest that a HMGB1/RAGE pathway may be associated with inflammation and particularly inflammation associated with GI disease in individuals with autism.

**Bibliography**


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