Immune-Glutamatergic Dysfunction as a Central Mechanism of the Autism Spectrum Disorders

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Abstract: Despite the great number of observations being made concerning cellular and the molecular dysfunctions associated with autism spectrum disorders (ASD), the basic central mechanism of these disorders has not been proposed in the major scientific literature. Our review brings evidence that most heterogeneous symptoms of ASD have a common set of events closely connected with dysregulation of glutamatergic neurotransmission in the brain with enhancement of excitatory receptor function by pro-inflammatory immune cytokines as the underlying mechanism. We suggest that environmental and dietary excitotoxins, mercury, fluoride, and aluminum can exacerbate the pathological and clinical problems by worsening excitotoxicity and by microglial priming. In addition, each has effects on cell signaling that can affect neurodevelopment and neuronal function. Our hypothesis opens the door to a number of new treatment modes, including the nutritional factors that naturally reduce excitotoxicity and brain inflammation.

Keywords: Autism spectrum disorders, excitotoxicity, fluoride, glutamatergic neurotransmission, inflammation, mercury, microglia, cytokines.

1. INTRODUCTION

We have witnessed an alarming increase in the incidence of ASD with rates increasing from 1 in 2,325 births prior to the 1980s to 1 in 101 births today. For male children, the incidence is now 1 in 67 births in some areas of the USA [1]. ASD are a group of related neurodevelopmental disorders, which includes autism, pervasive developmental disorder-not-otherwise specified (PDD-NOS), Asperger syndrome, Rett´s syndrome, and childhood disintegrative syndrome. The terms ASD and autism are used interchangably. ASD are characterized by a collection of neurobehavioral and neurological dysfunctions, often occurring before age 36 months [2-4]. Despite the great array of observations being made at the cellular and the molecular levels, no one has proposed an integrative and unifying mechanism to explain the heterogenous symptoms and etiology of ASD. Given the major role of glutamate in brain development, some authors have hypothesized that alterations of glutamatergic neurotransmission play a role in the pathophysiology of autism [5-10]. The hyperglutamatergic hypothesis of autism has been discussed recently [11, 12] focusing on findings of increased serum level of glutamate in children and adults with ASD [13, 9], the reduction of the levels of rate-limiting enzymes glutamate acid decarboxylase 65 and 67 (GAD65 and GAD67) and the increased gliosis in the brains of autistic subjects [14, 15].

A number of studies leave little question that there is a genetic propensity for autism risk. Studies showing higher incidence rates of 60 to 90% in monozygotic twins versus 0 to 6% in dizygotic twins suggest a herediability of over 90% [2]. Data from whole genome screening of multiplex families (having more than one autistic child) strongly suggest that 10 or more genes interact to cause classic autism [16]. Recent research of the autism genome supports further the view that abnormalities in genes connected with glutamate receptors (GluR) and regulation of glutamate pathways may be directly involved in ASD pathology [17]. A significant association between GluR6 gene, located on chromosome 6q21, and autism were found [5, 18, 19]. GluR6 genes control a member of the ionotropic receptor kainate family, which plays a major role in brain development. Strong evidence points to a mutation in chromosome loci 7q31 in both autism and language disorders [20]. The sequence on chromosome 11p12-13 has been linked to glutamate transport proteins. The neurexin-1 gene (*NRXN1)* has been shown to play a fundamental role in synaptogenesis and synaptic maintenance, as well as Ca^{2+} channel and NMDA receptor recruitment [21].

Serajee *et al.* [22] demonstrated from a study of 196 families having autistic children, a high incidence of mutation of the GRM8 gene controlling the metabotropic GluR8 receptor subunit, which negatively modulates glutamate neurotransmission. Mutation of this gene increases glutamate hyperactivity and thus excitotoxicity. This receptor subunit is located on a number of anatomical areas of the brain affected in autism, including the lateral reticular thalamic nucleus, pyriform cortex and to a lesser degree the cerebellum, caudate and hippocampus [23]. Ramanathan *et al.* [24] detected abnormalities in genes controlling AMPA receptors (GluR2) as well as glycine receptors (GLRA3 and GLRB), which play a critical role in inotropic GluR control, in a single case of autism. It is obvious from these studies that genetic influence on glutamate function is playing a role in the ASD.

In this paper we offer the explanation of potential etiology of ASD as dysregulation of glutamatergic neurotransmission, with underlying interactions between chronic microglial activation, and the excitotoxic cascade playing the central role. Table **1** gives observed alterations in ASD, which may be connected with dysfunctions of glutamatergic neurotransmission. Moreover, we suggest that the increasing prevalence of ASD during the last decades might reflect the

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