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Glutamatergic agents in Autism Spectrum Disorders: Current trends

Roberto Canitano *, Valeria Scandurra

University Hospital of Siena, Division of Child Neuropsychiatry, Viale Bracci 1 53100 Siena, Italy

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ABSTRACT

Glutamate transmission dysfunction has been found in various preclinical models of Autism Spectrum Disorders (ASD), thus the glutamate system is a target for therapeutics. This report reviews current treatments for glutamate dysfunction in ASD models and clinical trials. Antagonists of metabotropic glutamate receptor subtype 5 (mGluR5) have been tested in preclinical models of autism. Black and Tan Bachyuric (BTBR) mice model behavioral phenotypes of the three core diagnostic domains of autism, e.g. social deficits, impaired language and communication, and repetitive behaviors. A significant reduction in repetitive self-grooming was observed after mGluR5 antagonist administration in BTBR mice. SHANK 3 deficient mice which have altered synaptic transmission and plasticity, were administered IGF-1 treatment to reverse these deficits based on the hypothesis that reduced AMPA receptor levels reflect less mature synapses. Clinical trials have been carried out in ASD with glutamate NMDA receptors, but current findings are not sufficient for conclusions on safety and efficacy. Memantine is an NMDA antagonist under investigation in controlled trials that hopefully will provide new insight on its use in autism. Studies using novel treatments with other glutamatergic agents are also underway and encouraging results have been observed with N-acetylcysteine in treating irritability in ASD.

Contents

Abbreviations: ABC, Aberrant Behavior Checklist; CGI, Clinical Global Impression; VABS, Vineland Adaptive Behavior Scales; PL-ADOS, Pre-Linguistic Autism Diagnostic Observation Scale; CARS, Childhood Autism Rating Scale; LTD, Long Term Depression; LTP, Long Term Potentiation.

* Corresponding author. Tel.: +39 0577586512; fax: +39 0577586150.
E-mail addresses: canitano@unisi.it, r.canitano@ao-siena.toscana.it (R. Canitano).

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1. Introduction

Autistic spectrum disorders (ASD) are characterized by three core behavioral domains: social deficits, impaired language and communication, and repetitive behaviors (APA, 2000). A wide clinical heterogeneity, ranging from severe social and communication impairments to mild personality traits, awaits further definition in more precise clinical subgroups and phenotypes. Autistic disorder, childhood disintegrative disorder, pervasive development disorder not otherwise specified (PDD-NOS, or 'atypical autism'), and Asperger syndrome are all considered to be ASD. Current estimates of the prevalence of autistic disorder are around 20/10,000 and the prevalence for PDD not otherwise specified is around 30/10,000, according to current surveys. Recent studies examining the whole spectrum of PDDs have consistently provided estimates in the 60–70/10,000 range, making PDD one of the most frequent childhood neurodevelopmental disorders. The rise in the incidence of ASD during the past two decades is surprising and not fully understood. It might be explained by the use of broader diagnostic criteria, increased attention of the medical community and/or awareness, but a number of other factors, including environmental determinants, are under investigation (Fombonne, 2009).

Glutamate, the main excitatory neurotransmitter in the brain, has a leading role during development since it modulates neuronal formation and synaptic strengthening in the early phases and due to its primary role in neuronal plasticity and cognitive functioning (Lodge, 2009). Glutamate receptors are diffused throughout the brain and are widely represented in the cerebellum and hippocampus, regions implicated in ASD pathogenesis.

Glutamate signaling abnormalities are involved in the complex development of Autism Spectrum Disorders (ASD) as reported in several models, but many aspects are still unresolved. The pathways of abnormal glutamate transmission and the mechanisms leading to the specific clinical characteristics are still poorly understood (Carlson, 2012; Choudhury, Lahiri, & Rajamma, 2012). In particular, their role in influencing social and communication abnormalities, restricted interests and repetitive behaviors, the three core domains of ASD, is still not clear. The term autism will be used throughout the text as the abbreviation of ASD.

2. Glutamate in ASD

Glutamate activity is carried out through two types of receptors: metabotropic and ionotropic. Metabotropic glutamate receptors (mGluR), G-protein coupled receptors involved in intracellular signal transduction, can be divided into three groups: Groups I (mGluR 1 and 5), II (mGluR or mGluR 2 and 3) and III (mGluR 4 and 6–8). Group I receptors activate phospholipase C. Groups II and III are negatively coupled to cyclic AMP production, but they differ in agonist selectivity. Two types of Group III receptors, mGluR7 and mGluR8, are located within the pre-synaptic grid, whereas mGluR3 and mGluR2 are located on the pre-terminal axons (Kew & Kemp, 2005).

Ionotropic glutamate receptors form ligand gated ion channels and are labeled according to their prototypical agonists: NMDA (N-methyl-D-aspartate), AMPA and kainate. Six gene families encode all these receptors, of which AMPA receptors (GluR1–4), kainate receptors (GluR5–GluR7, KA-1 and KA-2) and NMDA receptors (NR1, NR2A-D and NR3A) are encoded by one, two and three gene families, respectively. AMPA receptors contribute to excitatory signaling and are implicated in Long-term Potentiation (LTP) and Long-term Depression (LTD), forms of synaptic plasticity associated with learning and memory. AMPA and NMDA receptors are responsible for post-synaptic density (Whitlock, Heynen, Shuler, & Bear, 2006). Kainate ionotropic receptors act presynaptically to decrease glutamatergic transmission in the hippocampus (Pinheiro & Mulle, 2006). Glutamate activation in the synapse is activated by excitatory amino acid transporters. The overstimulation of glutamate receptors results in neuronal damage and neurodegeneration through a mechanism known as excitotoxicity. Through the overactivation of glutamate receptors, particularly NMDAR receptors, high levels of calcium ions (Ca^{2+}) flow into post-synaptic cells causing a cascade of cell degradation processes ending in cell death (Sattler & Tymianski, 2001; Zhou, Hollern, Liao, Andrechek, & Wang, 2013). NMDA receptors (NMDARs) are the targets of the majority of current glutamatergic treatments in ASD. NMDARs are made up of multiple subtypes which differ in their subunit composition and pharmacological properties (Paoletti, Bellone, & Zhou, 2013). The involvement of different NMDAR subunits has been implicated in different forms of synaptic abnormalities, including those of ASD. However, the extent to which this involvement is domain and syndrome specific is still controversial and little is known about the role of each NMDAR subunit. Preclinical studies have provided evidence of NMDA receptor involvement in ASD. In a mouse model of ASD, a prenatal injection of valproic acid (VPA) caused an overexpression of NMDA receptor subunits NR2A and NR2B. The overexpression of NMDA receptor subunits translates into enhanced NMDA receptor-mediated synaptic currents. However, further investigations are required to determine whether NMDA receptors are truly up-regulated in this condition and to examine the role of this condition (Rinaldi, Kulangara, Antoniello, & Markram, 2007). Different findings have been observed in two paradigmatic examples of ASD. NMDA receptors were found decreased in FMRP knock out mice, thus Fmr1 deletion was implicated in a significant reduction of NMDA receptors and the resulting functional impairments (Eadie, Cushman,