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Developing Medications Targeting Glutamatergic Dysfunction in Autism: Progress to Date

Lawrence K. Fung, M.D., Ph.D and **Antonio Y. Hardan, M.D**

Division of Child & Adolescent Psychiatry, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine

Abstract

Pharmacologic treatments targeting specific molecular mechanisms relevant for autism spectrum disorder (ASD) are beginning to emerge in early drug development. This article reviews the evidence for the disruption of glutamatergic neurotransmission in animal models of social deficits and summarizes key pre-clinical and clinical efforts in developing pharmacologic interventions based on modulation of glutamatergic systems in individuals with ASD. Understanding the pathobiology of the glutamatergic system has led to the development of new investigational treatments for individuals with ASD. Specific examples of medications that modulate the glutamatergic system in preclinical and clinical studies are described. Finally, we will discuss the limitations of current strategies and future opportunities in developing medications targeting the glutamatergic system for treating individuals with ASD.

1. Introduction

Autism spectrum disorder (ASD) is a large public health issue, as evidenced by the rising prevalence, with an estimated rate of one in 68 children (age 8 years) in the United States in the latest study by the Centers for Disease Control and Prevention [1]. Effective pharmacologic treatments for core symptoms of the disorder (i.e., deficits in social communication, sensory aberrations, stereotypic behaviors, and restricted interests) are lacking. Part of this challenge may be due to the lag in translation of basic findings of the pathophysiology of ASD to clinically testable hypotheses. In the largest ASD whole exome sequencing (WES) study, genes involving three critical classes of molecular machinery for typical development are damaged – synaptic formation, transcriptional regulation and chromatin-remodeling [2]. The first two classes are also related to neurotransmission, which is controlled by excitatory and inhibitory systems. Glutamate is the most common excitatory neurotransmitter, and gamma aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter. One highly regarded model of ASD suggests that the condition is a result of an increased ratio of excitation to inhibition (E/I) in key neural systems [3]. The balance between brain levels of glutamate and GABA in each brain region controls the major inputs and outputs of neural circuits involved in essentially all physiological functions of the brain.

Address Correspondence to: Lawrence K. Fung, M.D., Ph.D., Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, California 94305-5717, Phone: (650) 723-5511, Fax: (650) 723-2269, lkfung@stanford.edu.

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Therefore, modulation of either the glutamatergic or GABAergic system is predicted to change the E/I ratio and may be considered as a strategy for treating symptoms in individuals with ASD. In this article, we will focus on the glutamatergic system in ASD. We will begin by providing a brief synopsis of the glutamatergic system, which will be followed by a review of the evidence on the association between the disruption of glutamatergic neurotransmission and the pathophysiology of ASD. In light of the relevance of the glutamatergic system, we will discuss the potential implications of modulating the glutamatergic system in the treatment of ASD, using specific drugs that affect the glutamatergic system and that have been explored in preclinical and/or clinical studies. Finally, we will conclude by discussing the potential pitfalls of current strategies as well as future opportunities in modulating the glutamatergic system for the treatment of core and associated features of ASD.

1.1. Glutamatergic Physiology

Glutamate is generated in the mitochondria of neurons from glutamine by glutaminase 1 and then transported into presynaptic vesicles via vesicular glutamate transporters (Vglut) or further metabolized to α-ketoglutarate by glutamate dehydrogenase as part of cellular metabolism (Fig 1). Glutamate is removed from the synaptic cleft by the glial transporter, excitatory amino acid transporter (EAAT1). In glial cells, glutamate is converted to glutamine and transported out by glutamine transporter (SN1), where it can be taken up by presynaptic excitatory neurons via neutral amino acid transporter (GLNT) and system amino acid transporter (SAT2). The glutamine is then converted back to glutamate by glutaminase (GLS) in the mitochondria to replenish the vesicular glutamate pool in the presynaptic terminal. Glial cells also contain glutamate decarboxylase 67 (GAD67) that converts glutamate to GABA. However, GABA released at neuronal synapses is primarily synthesized in the GABAergic interneuron.

Glutamate mediates excitatory neurotransmission via ionotropic and metabotropic receptors. There are three types of ionotropic glutamate receptors (Figure 1). The names of these receptors originated from the synthetic glutamate derivatives that activated the receptors: N-methyl-D-aspartate (NMDA), 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (AMPA), and kainate. Both NMDA receptors (NMDARs) and AMPA receptors (AMPARs) are composed of four subunits surrounding a central pore, with receptor properties varying depending upon exact channel composition. Metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors. mGluRs are divided into three groups (see Table 1) on the basis of their second messenger coupling and ligand sensitivity. Group I receptors (mGluR1 and 5) predominantly potentiate both presynaptic glutamate release and postsynaptic NMDAR currents. In contrast, group II (mGluR2 and 3) receptors, in general, limit glutamate release, particularly during conditions of glutamate spillover from the synaptic cleft. Like Group II receptors, Group III receptors (mGluR4, 6, 7, and 8) generally inhibit glutamate function. Overall, ionotropic glutamate receptors are involved in fast excitatory neurotransmission and Group I metabotropic receptors are responsible for slower excitatory neurotransmission, whereas Group II and III metabotropic receptors exert inhibitory neurotransmission.

In addition to the glutamate receptors, the dynamic interplays among these receptors and other molecular components such as adhesion proteins (e.g., neurexins (NRXNs), neuroligins (NLGNs), cadhedrins), scaffolding proteins (e.g., Shank 3), vesicle proteins (e.g., synapsin 1), and transporters (e.g., aspartate/glutamate carrier) are essential to maintain optimal glutamatergic neurotransmission. NLGNs are postsynaptic cell-adhesion molecules (CAMs) that are essential for proper synapse maturation and function. NRXNs are presynaptic CAMs that bind to NLGNs across the synaptic cleft. NLGNs bind to the postsynaptic density 95 (PSD95) that interacts with SHANK3 proteins.

2. Abnormalities of glutamatergic system in ASD

Given the many components of the glutamatergic system (and the other systems it interacts with), where do the abnormalities arise in ASD? The disruption of glutamatergic neurotransmission in individuals with ASD has been evidenced at the genetic, neurotransmitter levels, and receptor/protein levels. Furthermore, animal models of ASD have also provided support and tremendous insight into how the disruption of neural circuits is associated with aberrant behaviors.

In order to study the levels of glutamate receptors in the brain, investigators have employed postmortem approaches. Using postmortem brain samples of individuals with ASD, the glutamate receptor densities and protein levels were compared with samples of neurotypical individuals. The density of AMPA-type glutamate receptor was found to be decreased in the cerebellum of individuals with ASD [4]. Measurements of protein levels of metabotropic glutamate receptor 5 (mGluR5) revealed significant increases in the vermis of children with ASD [5]. To date, *in vivo* molecular imaging studies of glutamate receptors in ASD are lacking.

Concentrations of glutamate have been studied both peripherally and centrally. Increased peripheral levels of glutamate were found in both children [6–8] and adults [9] with ASD, compared to neurotypical controls. However, it is unclear if the elevated peripheral levels reflect central glutamate concentrations. Centrally, glutamate levels can be estimated *in vivo* in individuals with ASD by proton magnetic resonance spectroscopy (^{1}H-MRS). Current MRS technologies allow us to separate the spectral peaks of glutamate from other substances, with the exception of glutamine (and sometimes GABA), in defined brain regions of interest. The combined peak of glutamate and glutamine in the MR spectra is often denoted as the Glx peak. Compared to control participants, higher Glx levels were found in the right hippocampus [10], anterior cingulate gyrus [11, 12], and auditory cortex [13] of individuals with ASD. However, the Glx levels in the thalamus of high-functioning adults [14] and children [15] with ASD were found to be indistinguishable from their neurotypical counterparts. A recent study found that Glx-to-creatine ratio in the thalamus was positively related to the social interaction score of the Autism Diagnostic Interview™ – Revised (ADI-R) in children with ASD [16]. Interestingly, the Glx levels (normalized by creatine levels) were found to be lower in the frontal lobes of children and adolescents with ASD compared to neurotypical controls [17]. Overall, despite the replicated elevation of glutamate levels in individuals with ASD, the results for central Glx levels determined by MRS are mixed. For more detailed review, please see Rojas et al. [18].

Various genome wide association studies (GWAS) have uncovered the association between genes involved in glutamatergic neurotransmission and ASD (Table 2). *GAD1*, which encodes for GAD67, was found to be a candidate gene for ASD in one linkage study [19]. However, other investigations did not replicate this finding [20]. *GRIN2A* and *GRIN2B* encoding for the NR2A and NR2B subunits of NMDA receptors were found to be associated with ASD in whole exome sequencing studies [2, 21]. In addition, many genes expressing molecular components related to the glutamatergic synapses have been found to be associated with ASD (Table 2). NRXNs and NLGNs are CAMs that are essential for synapse formation and function [22]. *NLGN1*, *NLGN3*, and *NLGN4* localize to excitatory synapses, whereas *NLGN2* localizes primarily to inhibitory synapses. Point mutations, translocation events, and deletions in *NLGN1*, *NLGN3*, and *NLGN4* were found in rare cases of ASD [23–27]. Similarly, genes encoding neurexins (*NRXN1*, *NRXN2* and *NRXN3*) were also found to be associated with ASD in large-scale linkage studies [28–32]. Within the *NRXN* superfamily, *CNTNAP2* may be regarded as the most prominent member. *CNTNAP2* is involved in clustering potassium channels at the nodes of Ravier in myelinated axons, as well as neuron–glia interactions. *CNTNAP2* has been found to be associated with language development delays in children with ASD [33–36]. In addition to CAMs, scaffolding proteins such as PSD95 are known to play an important role in synaptic plasticity [37]. For example, PSD95 anchors synaptic proteins, including NLGN, NMDA receptors, AMPA receptors, and potassium channels [38]. Variations of *DLG4* (encoding PSD95) were found to associate with reduced intraparietal sulcus volume and abnormal cortico-amygdala coupling [39], which are manifested in individuals with ASD.

3. Current evidence of efficacy for glutamatergic agents in the treatment of ASD

Based on some of the evidence discussed above, investigators have started exploring pharmacologic treatments of common symptoms exhibited in ASD both pre-clinically and clinically. Below, we will describe the studies targeting the NMDAR, AMPAR/KR, mGluRs, as well as other relevant mechanisms in the glutamatergic system.

3.1. NMDA receptor partial agonists and antagonists

D-Cycloserine, a partial agonist of NMDAR, has been shown to ameliorate social alterations [40–44] and spontaneous stereotypic behaviors [41] in various mouse models of ASD. In a 2-week, pilot, single-blind placebo lead-in study with children, adolescent and young adults with ASD (N=10; mean age 10.0±7.7; range 5–28 years), D-cycloserine resulted in significant improvement in the social withdrawal subscale of the Aberrant Behavioral Checklist (ABC-SW) [45]. In a double-blind randomized, 10-week pilot study (N=20; age range 14–25 years), the result on improvement in ABC-SW by D-cycloserine was not replicated [46]. However, D-cycloserine was found to reduce stereotypic symptoms (as measured by stereotypy subscale of the ABC) in young adults and adolescents [46].

Amantadine is a NMDAR antagonist that has been used to treat Parkinson’s disease [47]. In a 4-week, double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with ASD (N=43; mean age 7; range 5–15 years), the amantadine-

treated group was found to have statistically significant improvements in clinician-rated (but not parent rated) ABC subscales for hyperactivity and inappropriate speech [48].

Memantine is another NMDAR antagonist that has been used to treat Alzheimer's disease [50]. A retrospective study of memantine in children and adolescents with ASD (N=18; mean age 11.4±3.3; range 6–19 years) showed improvement in Clinical Global Impressions – Improvement (CGI-I) [51]. A prospective, 8-week, open-label trial of memantine in children with ASD (N=14; mean age 7.8±1.8 years) showed significant reductions in multiple ABC subscales, including hyperactivity, lethargy, and irritability [52]. A large 48-week, randomized controlled trial was completed examining the efficacy of memantine in children with autism (N=747; mean age 9.1±1.9 years), but unpublished report indicate that there was no evidence of benefit with this medication in this trial [54].

Riluzole is another NMDAR antagonist [55] that was approved to treat patients with amyotrophic lateral sclerosis [56]. A case series of the use of riluzole as an adjunctive treatment in children with ASD (N=3; age range 15–20 years) has shown improvement in CGI scores [57].

Acamprosate is also a NMDAR antagonist that has been used for maintaining abstinence from alcohol in patients with alcohol dependence [59]. A pilot single-blind placebo lead-in study of acamprosate in youth with ASD (N=15; mean age 10.4; range 5–15 years) demonstrated that the medication reduced various ABC subscale scores including hyperactivity and social withdrawal [60]. A pilot analysis in fragile X syndrome (FXS)-associated ASD also suggested that reduction in amyloid-β precursor protein (APP) may be a novel pharmacodynamic property of acamprosate [60].

3.2. AMPA/kainate antagonists

Topiramate is an antagonist of AMPAR/KR [61]. In addition, it is also an agonist of $GABA_A$ receptors, and an inhibitor of voltage-gated sodium channels, high-voltage-activated calcium channels, as well as specific isoforms of carbonic anhydrase. Topiramate as an adjunctive pharmacologic agent was retrospectively studied in children with ASD (N=15; mean age 14.7±3.3 years), and was found to be potentially useful in treating secondary symptoms of ASD, including inattention, hyperactivity and conduct behaviors [62].

3.3. mGluR5 antagonists

Antagonists of mGluR5 have been studied extensively in fragile X syndrome (FXS), the most common genetic cause of ASD [64] and inherited cause of intellectual disability [65]. The mutation responsible for FXS consists of trinucleotide CGG repeats (>200) within the *FMR1* gene on the long arm of the X chromosome. The expansion of CGG repeats leads to DNA hypermethylation within *FMR1*, resulting in its transcriptional silencing, and therefore the absence or attenuation of the gene product, *FMR1* protein (FMRP). The general prevalence of males with a full mutation of the affected gene *FMR1* is estimated as 1 in 4000, while the female prevalence is approximately 1 in 5000–8000 [66]. Approximately 20–50% of individuals with FXS meet the diagnostic criteria for ASD [67–69]. Individuals

with FXS exhibit deficits in executive function [70], gaze aversion, increased social anxiety, social avoidance [71], as well as impairments in visuospatial processing.

A 3-week treatment with a specific mGluR5 antagonist, AFQ056, was able to restore sociability behavior of *Fmr1* knockout mice (an animal model of ASD and FXS) to levels of wild type littermates. These results support the importance of mGluR5 signaling pathways on social interaction behavior and that AFQ056 might be useful as potential therapeutic intervention to rescue various behavioral aspects of the fragile X phenotype [72]. However, in the first randomized, double-blind (two-treatment (4 weeks each), two-period, crossover study) study of a mGluR5 antagonist, AFQ056, in adult patients with FXS [N=30; mean age 25–26, range 18–36 years], the compound failed to show improvement in the primary behavioral endpoint [ABC – Irritability Subscale (ABCI)] [73]. Several other mGluR5 antagonists (e.g. RO4917523 [74] and STX107) are being tested in individuals with FXS.

3.4. Other agents targeting the glutamatergic system

N-acetylcysteine (NAC) is a glutamatergic modulator as well as an antioxidant. Clinically, NAC is best known as the antidote for acetaminophen overdose. More recently, this medication has been shown to be efficacious in randomized controlled trials in neuropsychiatric disorders, including trichotillomania [75], bipolar disorder [76], and schizophrenia [77]. In a 12-week, double-blind randomized, placebo-controlled study of NAC in children with ASD (N=29), this compound was found to be well-tolerated and effective for targeting irritability and associated behaviors in ASD. In addition, data from this study also suggested that NAC might improve stereotypic/repetitive behaviors in this population [78].

Medications targeting specific targets of the glutamatergic system are represented in Figure 2. Overall, preliminary evidence for the utility of pharmacologic agents targeting components of the glutamatergic system (NMDA, AMPA/kainate, and mGlu receptors) in the treatment of behavioral symptoms (irritability, stereotypic behaviors, and hyperactivity) in individuals with ASD is emerging. In order to confirm these results, randomized controlled trials are needed to replicate these findings. In the remaining sections, we will discuss the limitations of current methods and future opportunities in developing compounds for the treatment of symptoms present in individuals with ASD.

4. Limitations to current strategies

Despite the potentially encouraging preliminary findings of the above clinical trials, current methodologies to develop treatments for individuals with ASD are limiting. First of all, ASD is a very heterogeneous disorder with many potential etiologies including those where a glutamatergic dysfunction might not play a key role in the pathophysiology. Treatments targeting a specific molecular component of the glutamatergic system are likely to benefit only a subset of the ASD population. Therefore, we expect that most individuals with ASD who do not have deficits in the glutamatergic system are less likely to respond. As a result, the probability for successfully treating the general ASD population without stratifying for deficits in the glutamatergic system is expected to be low. A second limitation of current medication trials is the use of behavioral endpoints as the primary outcome measures. These

endpoints are often determined by subjective informant-based questionnaires instead of objective biological measures relevant to a specific molecular mechanism. Specifically, after the successful use of the ABC-I as the primary outcome measure for the treatment of severe tantrums, aggression, or self-injurious by risperidone [79], the ABC-I has become a gold standard in measuring irritability and associated aggressive behaviors in clinical trials for the ASD population. While the ABC-I will continue to be very helpful to determine behavioral efficacy, it is important to note that objective assessments of the mechanism of action should be central in the development of treatments targeting specific biological targets. Thirdly, clinical trials can fail because of improper dose selection. Due to the high costs of clinical trials, many novel medications were tested at the maximum tolerated dose (MTD). The MTD is chosen at the highest dose with no significant severe adverse events. While this approach may be appropriate for novel medications in other therapeutic areas, it is inadequate for most central nervous system targets [80]. For example, many glutamate receptors require partial activation for effective stimulation due to down-regulation at full occupancy. Therefore, doses above the effective range may result in lack of efficacy. Finally, the developmental perspective of ASD as a neurodevelopmental disorder has not been fully appreciated and incorporated in the drug discovery and development process. For example, imaging studies of toddlers with ASD have shown that the neuroanatomy of these children was distinctly different from neurotypical controls and idiopathic intellectual disability [81]. Therefore, accounting for the impact of development on neuroanatomy and consequently on neural circuits mediating the pathophysiology of ASD will provide us with opportunities to understand when and what to target.

5. Future Directions

Targeting specific molecular targets can be an attractive tactic but we need neural-based biomarkers to develop treatments for diseases in psychiatry. Molecular mechanisms, such as the glutamatergic and GABAergic systems, appear to be good starting points for developing more specific biological treatments for ASD. As discussed above, a main challenge in studies conducted to date is the non-specific nature of behavioral endpoints (ABC-I) and the lack of measures that are sensitive to change. As we march toward the future of neuroscience-based psychiatric research, we will need to consider using more objective neural based recruitment criteria and endpoints to track treatment effects. For example, molecular imaging can be used to generate biomarkers for selecting research participants based on their neural phenotype; it can also be used to track treatment progression. This approach has been employed successfully in the development of new investigational agents for Alzheimer’s disease [82]. In addition to molecular imaging, multi-modal magnetic resonance imaging (MRI) may also yield neural-based biomarkers.

Neurodevelopmental trajectories are key to understanding neuropsychiatric diseases and developing the next generation of treatments. We anticipate that one of the next steps to advance our understanding of brain development is to supplement our knowledge of anatomical neurodevelopment by charting the developmental course of molecular targets relevant to specific ASD subtypes. If abnormalities in structural and/or molecular brain biomarkers can be detected early in life (e.g. infancy), we may be able to prevent “at risk”

brains from further developing abnormal neurocircuits by intervening early when the brain is most plastic.

Inasmuch as we expect novel pharmacologic treatments will yield new interventions for individuals with ASD by modulating the pathophysiologic processes responsible for ASD symptoms, medication treatments alone may not result in most favorable outcome without behavioral treatments. Experience-dependent neuroplasticity is a well-known phenomenon in neuroscience [83] and is key in neurodevelopmental disorders in general and in ASD in particular. In *Fmr1* KO mice, environmental enrichment (EE) was shown to enhance expression of the AMPA receptor subunit GluR1 in the visual cortex, increase dendritic branching, spine number, and appearance of mature spines, and rescue alterations in exploratory behavior [84]. Furthermore, animal models of other brain disorders such as Down syndrome and Alzheimer's disease have also shown the utility of EE in restoring a myriad of behavioral functions [83]. While EE works by modulating experience-dependent neuroplasticity in animals, we predict that cognitive-behavioral interventions may modulate the same process in humans with ASD and other neuropsychiatric disorders. In the future, for infants and toddlers identified with specific subtypes of ASD defined by molecular and circuit abnormalities, pharmacologic treatments will be utilized to modulate neuroplasticity while cognitive-behavioral treatments will be used to habilitate these individuals who have never acquired the neural architecture underlying adaptive cognitive-behavioral functions. For those who have already developed symptoms, the goal of intervention will be to reverse their symptoms. Collectively, we anticipate that targeted molecular and circuit-based pharmacologic treatments combined with cognitive-behavioral interventions will likely have the highest potential to enhance neuroplasticity and improve therapeutic outcomes. We have high hopes that novel medications modulating the glutamatergic system will become part of future molecular and circuit-based pharmacologic treatments for individuals with ASD.

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Key Points

- Dysfunction of the glutamatergic system represents a potential pathophysiologic mechanism responsible for behavioral manifestations in autism spectrum disorder (ASD).
- Recent pre-clinical and clinical investigations of glutamatergic agents are encouraging. However, clinical testing continues to present significant limitations – for example, heterogeneity of ASD population, and reliance of relatively subjective informant-based rating scales instead of objective biological measures of the glutamatergic system.
- In the future, approaches to monitor molecular mechanisms of medication response (for example, by positron emission tomography and magnetic resonance spectroscopy) may help in developing medications targeting the glutamatergic system and other specific mechanisms relevant for ASD.

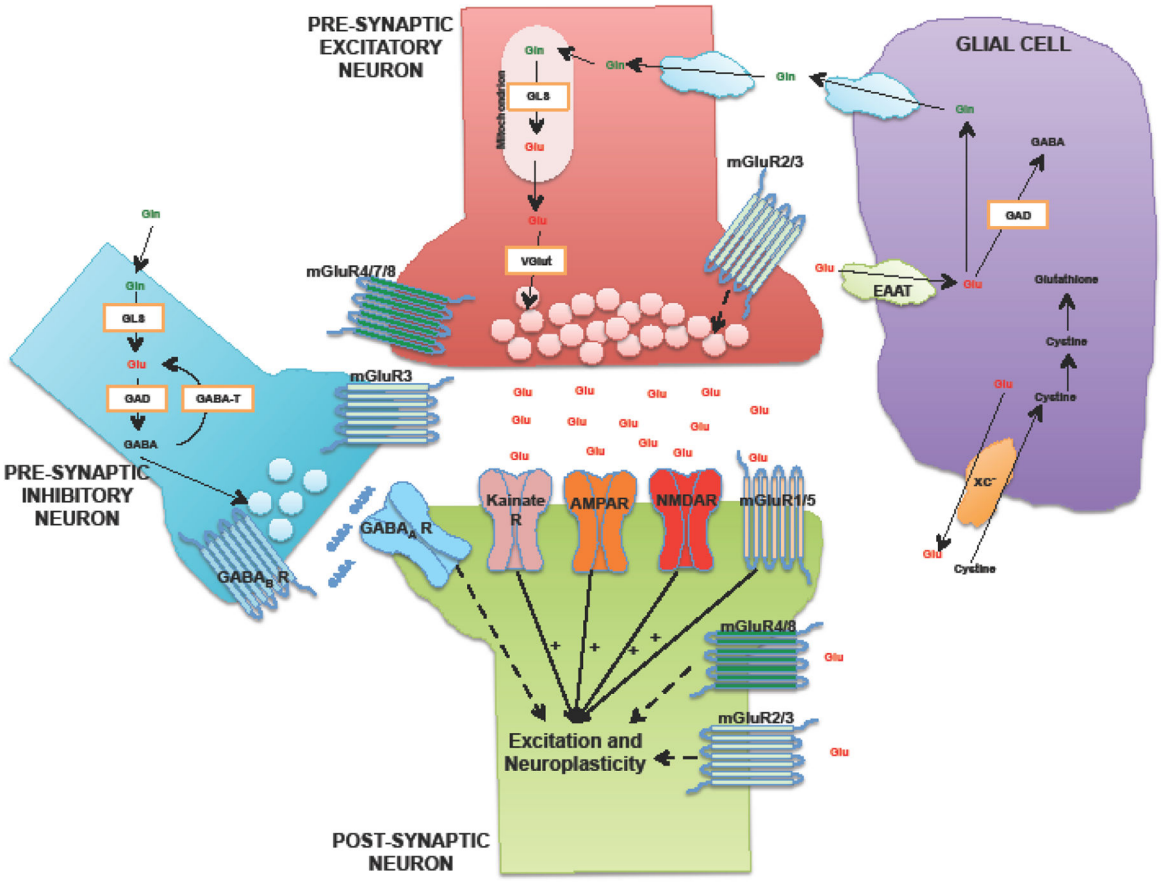

Figure 1.

Major receptors amenable to therapeutic manipulation in the glutamatergic synapse. NMDA and AMPA-type glutamate receptors, type 1/5 of metabotropic glutamate receptors, and XC^- antiporter are major targets for current pre-clinical and clinical investigations in the treatment of individuals with autism spectrum disorder. Please see text for detail description of the glutamatergic synapse.

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAAT, excitatory amino acid transporter; GABA, γ-aminobutyric acid; GAD, glutamate decarboxylase; GLS, glutaminase; Glu, glutamate; Gln, glutamine; GLUD1, glutamate dehydrogenase; mGluR, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartate; Vglut, vesicular glutamate transporter; XC^-, cystine/glutamate antiporter.

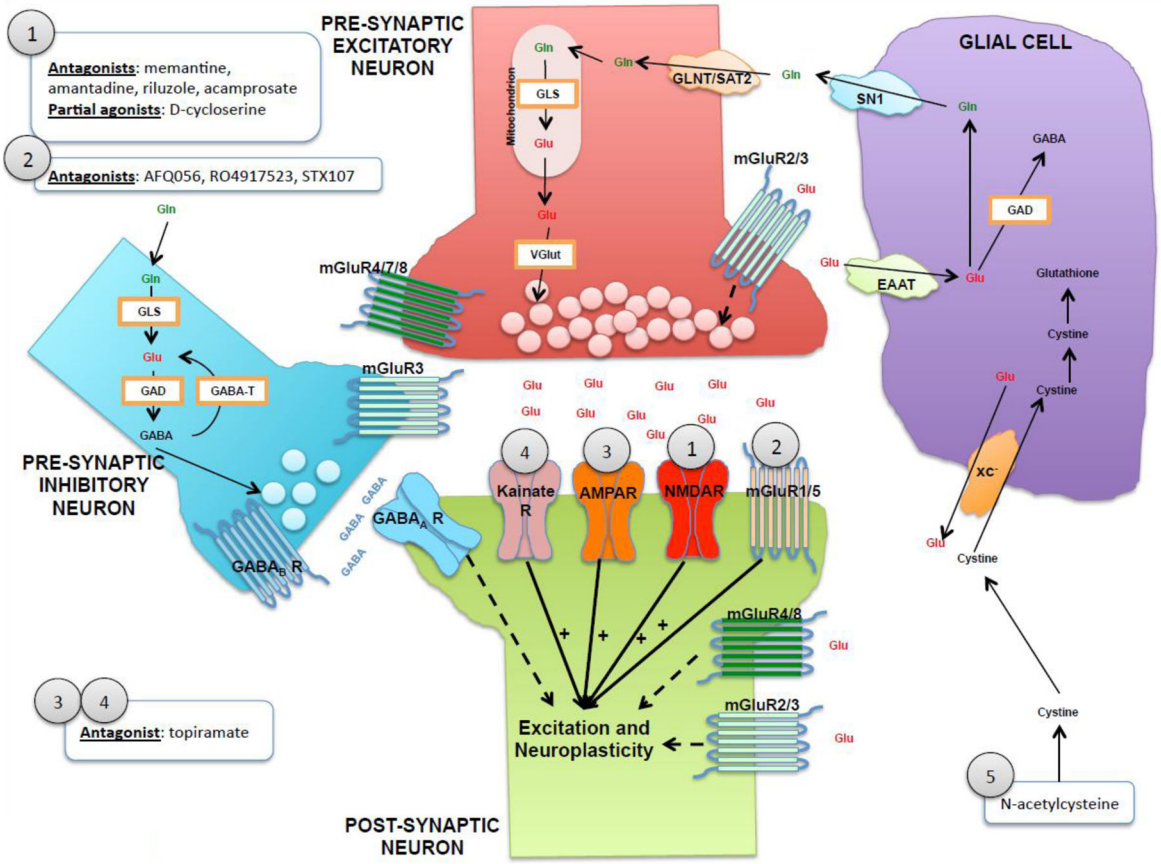

Figure 2.

Potential pharmacological targets for the treatment of autism spectrum disorder. Numbers identify loci of action of pharmacological compounds targeting components of the glutamatergic system: (1) NMDR-type glutamate receptors (NMDAR), (2) type 1/5 metabotropic glutamate receptors (mGluR1/5), (3) AMPA-type glutamate receptors (AMPAR), (4) kainate receptors, and (5) XC^{-} antiporter.

Table 1

Classification of glutamate receptors

	Group	Sub-type	Subunits	Function
Ionotropic	NMDA	"NR1-NR2"	NR1	Fast excitatory
			NR2A	
			NR2B	
			NR2C	
			NR2D	
		"NR1-NR3"	NR1	
			NR3A	
			NR3B	
	AMPA		GluR1	
			GluR2	
			GluR3	
			GluR4	
	Kainate		KA1	
			KA2	
			GluR5	
			GluR6	
			GluR7	
Metabotropic	Group I	mGluR1		Slow excitatory
		mGluR5		
	Group II	mGluR2		Slow inhibitory
		mGluR3		
	Group III	mGluR4		
		mGluR6		
		mGluR7		
		mGluR8		

Table 2

Genes and proteins important for optimal functioning of glutamate receptors and associated with autism spectrum disorder.

Gene	Protein	Loci	Protein Function	Reference
CDH8	Cadhedrin	16q21	Glycosylated transmembrane proteins that	[85]
CDH9	Cadhedrin	5p14.1	mediate cell–cell adhesion, neuronal migration,	[86]
CDH10	Cadhedrin	5p14.1	spine morphology, synapse formation, and	[86]
CDH13	Cadhedrin	16q23	synaptic remodeling	[87]
CNTNAP2	Contactin-associated protein-like 2 (CASPR2)	7q35-q36	Transmembrane scaffolding protein involved in the clustering of Kv1.1 at the nodes of Ranvier.	[33–36]
DLG4	PSD-95	17p13.1	Regulation of localization and trafficking of AMPA receptors	[39]
DYRK1A	Dual-specificity tyrosine phosphorylation-regulated kinase (DYRK)	21q22.13	DYRK1A-dependent phosphorylation of NR2A hinders the internalization of NR1/NR2A, causing an increase of surface NMDA receptor density	[88]
GAD1	GAD67	2q31.1	Catalyzes the conversion of glutamic acid to GABA	[19]
GRIN2A	NR2A of NMDAR	16p13.2	NR2A subunit of NMDA receptor	[21]
GRIN2B	NR2A of NMDAR	12p13.1		[2]
NRXN1	Neurexin	2p16.3	Synaptic adhesion proteins that are located on the presynaptic membrane and bind to their postsynaptic counterpart, neuroligins.	[28–31]
NRXN2	Neurexin	11q13		[31]
NRXN3	Neurexin	14q31		[32]
NLGN1	Neuroligin	3q26	Synaptic adhesion proteins that are located on the postsynaptic membrane and bind to their presynaptic counterpart, neurexins.	[23, 24]
NLGN3	Neuroligin	Xq13		[23, 25, 26]
NLGN4	Neuroligin	Xp22.3		[23, 27]
PCDH9	Protocadhedrin	13q21.32	The largest subgroup of the cadherin superfamily (see above) of homophilic cell-adhesion proteins.	[89]
PCDH10	Protocadhedrin	4q28.3		[89]
SLC25A12	AGC1	2q24-q33	Catalyze the exchange of aspartate for glutamate and a proton; involved in the malate/aspartate NADH shuttle; involved in the urea cycle.	[90]
SHANK3	Shank 3	22q13.3	Synaptic scaffolding proteins that bind neurexin-neuroligin and NMDAR complexes at the PSD of excitatory glutamatergic synapses	[91–93]
SHANK2	Shank 2	11q13.3-q13.4		[30, 94]
SHANK1	Shank 1	19q13.33		[95, 96]
SYNAPSIN 1	Synapsin 1	Xp11.23	Presynaptic phosphoproteins that account for 9% of the vesicle protein and can regulate neurotransmitter release and neurite outgrowth.	[97]
SYNAPSIN 2	Synapsin 2	3p25.2		[98]
SYNGAP1	SYNGAP1	6p21.32	Suppresses signaling pathways linked to NMDAR- mediated synaptic plasticity and AMPAR membrane insertion	[2]
TAOK2	TAOK2	16p11.2	A kinase involved in membrane blebbing and the MAPK14/ p38MAPK stress-activated MAPK cascade.	[99]

Abbreviations: AGC1, Mitochondrial aspartate/glutamate carrier; AMPA, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid; DYRK, Dual-specificity tyrosine phosphorylation-regulated kinase; GABA, gamma aminobutyric acid; MAPK, mitogen-activated protein kinase; NADH, nicotinamide adenine dinucleotide; NMDA, N-methyl-D-aspartate; PSD, postsynaptic density; SYNGAP1, synaptic Ras-GTPase-activating protein 1; TAOK2, thousand-and-one-amino acid 2 kinase