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Glutamate receptor dysfunction and drug targets across models of autism spectrum disorders

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ABSTRACT

There is strong evidence that metabotropic and ionotropic glutamate receptors are affected in autism spectrum disorders (ASD), but there are few candidate genes indicating involvement of these receptors. This suggests that glutamate receptor dysregulation may primarily be involved in the expression of ASD, but is an uncommon etiology. Directly implicated in models of fragile-X with ASD phenotypes is metabotropic glutamate receptor type 5 (mGluR5), which appears to be an effective pharmacologic target in a number of models of ASD. The review of other ASD models demonstrates that there is also evidence of a role for kainate, NMDA, and AMPA receptors in the neuropathophysiology of ASD, though the relationship between dysfunction in those receptors and ASD-associated phenotypes is not well understood. Current models indicate a way forward to delineate the role of glutamate receptors in ASD. Further development of preclinical models focusing on glutamate receptors may provide tools to target a clinically important subset of ASD symptoms.

1. Introduction

A diagnosis of ASD is determined from the presence of core deficits in 1) communication, 2) social, and 3) repetitive behaviors; with changes in social behavior and inappropriate repetitive activity being the most easily measured in rodent models (Brodkin, 2008; Crawley, 2007; Korff and Harvey, 2006). ASD is also associated with clinically important common co-morbidities, which include anxiety, epilepsy, and intellectual disabilities. In the context of ASD, development of treatments over and within each of these domains has been hampered by the paucity of validated models of ASD.

Glutamate is the most common neurotransmitter, mediating fast-excitatory transmission in mammalian systems via AMPA and Kainate receptors (Lodge, 2009). At NMDA and metabotropic glutamate receptors (mGluR), glutamate also engages intracellular transduction mechanisms in neurons and glia to provide a broad regulatory impact on neuronal homeostasis, local and nuclear transcription, synaptic plasticity, and neuronal development. Disruption in the balance between excitation and inhibition is a commonly proposed disease mechanism in ASD, as well as in the common ASD co-morbidity of epilepsy (Orekhova et al., 2007; Polleux and Lauder, 2004). Glutamatergic synaptic transmission through AMPA receptors provides the excitatory pole of this balance. Linking NMDA and metabotropic receptors to AMPA receptor activity are a number of synaptic plasticity mechanisms, where glutamate-evoked intracellular signaling modulates AMPA-dependent excitatory strength, via regulation of AMPA receptor cycling into the synaptic membrane (Bruneau et al., 2009; Svitkina et al., 2010). Reduced AMPA receptor density is associated with ASD in human patients (Purcell et al., 2001).

Perhaps surprisingly, there is only one strong glutamate receptor gene candidate for ASD in the kainate receptor family. (Jamain et al., 2002; Shuang et al., 2004; Strutz-Seebohm et al., 2006). However, as discussed below, glutamate transmission abnormalities are common in models of ASD. How specific glutamatergic dysfunction may lead to specific core- and associated-symptoms of ASD is not fully understood, nor are the therapeutic rationales for targeting glutamatergic systems well developed. Thus, in the face of limited effective treatments for ASD, additional tools to research the role of glutamate receptors in ASD are needed.

To review the present utility of models to enlighten the role of the glutamate system in ASD, we will first discuss preclinical models designed with transgenic construct validity for disruption of glutamatergic transmission. The balance of our discussion reviews models that recapitulate features of ASD that may in turn be relevant for delineating a relationship between ASD related phenotypes and glutamate receptor dysfunction. Finally, we briefly speculate on new directions in model development targeted at the glutamatergic system in ASD.

2. Modeling genetic candidates of ASD: GluR6

ASD candidate genes, coding for proteins directly involved in glutamatergic transmission, are rare, yet a subunit of the Kainate receptor GluR6 was identified as a strong candidate gene (Jamain et

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al., 2002; Shuang et al., 2004; Strutz-Seebohm et al., 2006). These findings were most recently replicated in European- and Korean-derived populations (Holt et al., 2010; Kim et al., 2007). Along with AMPA receptors, kainate receptors make up the fast-ionotropic glutamate receptors and are differentiated into subtypes by the presence of GluR5 or GluR6. While a minor contributor overall, kainate receptors provide important sources of excitatory drive, particularly in interneurons, and they are also implicated in some forms of plasticity (Fisahn et al., 2004; Kullmann and Lamsa, 2008; Rodriguez-Moreno and Sihra, 2007). Kainate receptors can also have metabotropic activity that may mediate some of its actions (Fisahn et al., 2005; Rodriguez-Moreno and Sihra, 2007). GluR6-containing receptors also strongly modulate gamma-band EEG activity, an area of growing interest clinically and preclinically in ASD (Fisahn et al., 2004; Gandal et al., 2010; Rojas et al., 2008; Wilson et al., 2007). Mice without GluR6 showed reduced susceptibility to seizures and appeared less anxious, indicating that GluR6 may have a role in ASD co-morbid symptom domains of anxiety and epilepsy (Shaltiel et al., 2008). One of the polymorphisms linked to ASD as well as to obsessive–compulsive disorder (OCD; M8361) appears to produce a gain of function, with this polymorphism generating larger kainate-induced currents (Shuang et al., 2004). In contrast to the GluR6 KO mice, such a gain of function could be predicted to be anxiogenic, affect gamma-band activity, and increase seizure susceptibility and OCD-like behavioral correlates. Thus, the generation of mice carrying a knocked-in M8361 allele may provide a useful tool for preclinical drug development targeting abnormal GluR6-mediated activity in ASD.

3. Fragile-X, FMR1 and the mGluR5 hypothesis of ASD

Fragile X is a leading cause of inherited intellectual disabilities and is associated with the presence of various social disabilities that, in some cases, lead to diagnoses of ASD. Models developed in a number of systems to understand and test mechanisms of fragile-X are exemplary for identifying a role for metabotropic glutamate receptors (mGluR) in ASD (Bear et al., 2004). Fragile X was identified as a chromosomal abnormality with a number of genes potentially involved, but the specific disruption of the gene FMR1 (coding for the fragile-X mental retardation protein 1) has been strongly implicated in the syndrome (Kaytor and Orr, 2001). Nearly three decades of research have generated a strong molecular, neurodevelopmental and synaptic story that describes how reduced FMR1 leads to a loss of mRNA translational repression, allowing an upregulation of type 5 metabotropic glutamate receptor (mGluR5) activity (Bear et al., 2004; Kaytor and Orr, 2001). This increased mGluR5 activity underlies some of the symptomatology of fragile-X in model systems (Westmark et al., 2009; Yan et al., 2005; but see Dahlhaus and El-Husseini, 2010). This work has advanced to clinical trials with mGluR5 antagonists in fragile-X patients (Dolen et al., 2010).

Much of this mGluR5 hypothesis of fragile-X was established by disrupting FMR1 in mice, zebrafish and *Drosophila* (Bardoni and Mandel, 2002; den Broeder et al., 2009; McBride et al., 2005; Morales et al., 2002; Tucker et al., 2006; Wan et al., 2000) These models identified the molecular mechanism of FMR1 as a local suppressor of mRNA translation, leading to altered dendritic morphology, reduced excitatory potentials, and disrupted synaptic plasticity (well reviewed in (Bear et al., 2004; Dolen and Bear, 2008). On the behavioral level, face validity for core features of ASD, mice and *Drosophila* models with deleted FMR1 showed impaired social interactions (McBride et al., 2005; McNaughton et al., 2008; Mineur et al., 2006). FMR1 KO mice also demonstrated increased seizure susceptibility and anxiety — two areas also associated with fragile-X and ASD (El Idrissi et al., 2005; McNaughton et al., 2008; Musumeci et al., 2007; Westmark et al., 2009).

Increased mGluR5 activity in the FMR1−/− mouse led to the prediction that mGluR5 antagonist may rescue some of these phenotypes. Indeed, chronic treatment with the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP), can rescue morphological and synaptic phenotypes, while reducing anxiety and seizure phenotypes, yet the core ASD features comprising social deficits are resistant to MPEP rescue (de Vrij et al., 2008; Meredith et al., 2010; Suvrathan et al., 2010; Yan et al., 2005). In contrast, FMR1 rescue itself does reverse social deficits (Spencer et al., 2008). These data first established a theme that glutamatergic dysfunction may primarily impact specific symptom domains within the core- and associated-ASD features. These include anxiety, seizure susceptibility and, as we will discuss below, repetitive behaviors. Additional evidence indicates that chronic MPEP treatment efficacy in FMR1 mice models is developmentally dependent, suggesting that glutamatergic dysfunction has a role in the developmental etiology of fragile-X (Meredith et al., 2010). While mGlur5 antagonists do not appear to be a magic bullet for fragile-X or ASD treatment, their ability to combat anxiety and reduce the increased risk for epilepsy associated with these disorders, may be clinically significant in treating ASD.

4. Indirect impact on glutamatergic system

4.1. Disruption of synaptic proteins in excitatory synapses

In the case of GluR6 and FMR1 abnormalities, glutamate receptor disruptions are directly implicated. An indirect, but strong case for examining glutamate receptors and synapses in models of ASD is the gathering evidence for disruption synapse development and homeostasis in ASD. (Betancur et al., 2009; Zoghbi, 2003). This evidence is supported by studies linking a large family of candidate genes to ASD, which are involved in the plasticity, maintenance, and development of excitatory synapses. These candidate genes include the presynaptic factors neurexin-1 as well as neuregulins-1, 3 and 4; members of the trans-synaptic matrix, neural cell adhesion molecule-2 (NCAM2); and, post-synaptically, neuroligins, the synaptic-scaffolding proteins (Shank1-3), as well as the post-synaptic density protein, PSD95 (Berkel et al.; Betancur et al., 2009; Blundell et al., 2010; Etherton et al., 2009; Feyder et al., 2010). Additionally, the VPA, MeCP2−/−, and fragile-X models demonstrate disruption of synaptic ASD candidate proteins such as neuroligin 3 (Dahlhaus and El-Husseini, 2010; Gandal et al., 2010; Kolozsi et al., 2009). When these synaptic proteins are transgenically disrupted in mice, the most common behavioral impact is increased stereotypies and signs of anxiety, though in some models social deficits are also found (see: Table 1; Blundell et al., 2010; Etherton et al., 2009; Feyder et al., 2010). Probing synaptic transmission in these models also often implicates reduced AMPA- and NMDA-dependent glutamatergic transmission. As in fragile-X, there is also pharmacological evidence for treating some of the behavioral outcomes found in models of these protein-specific dysfunctions with mGluR5 antagonists.

4.2. mGluR5

The potential clinical efficacy of NMDA and mGluR5 agents in ASD and PPDs arises from the evidence that disruption of glutamatergic transmission may be a general mechanism underlying at least some of the symptoms in ASD (Silverman et al., 2010a). Because mGluR5 is linked with synaptic plasticity and is critical to the appropriate development and maintenance of excitatory synapses in the CNS, it is a reasonable candidate (Simonyi et al., 2005; Spires et al., 2005). Following this line of reasoning, Jackie Crawley's group tested MPEP in the BTBR mouse (Silverman et al., 2010a). The BTBR mouse is a model of insulin resistance that has demonstrated strong face validity for ASD core symptoms of repetitive behaviors and reduced sociability

Table 1
Selected ASD mouse models that demonstrate a role for glutamate receptors. These models include four examples of disrupted synaptic adhesion or scaffolding proteins. Themes of disrupted excitatory transmission, linked with repetitive behavior and increased anxiety are common among these models. Social deficits associated with these models appear resistant to glutamate receptor agents.

ASD Model	Construct validity	Face validity: ASD core domains	Face validity: ASD-associated symptoms domains	Evidence for disrupted glutamate receptor activity	References
GluR6−/− (GRIK2)	Candidate gene		Decreased anxiety, reduced seizure susceptibility	KO directly removes a primary subunit of Kainate receptor type 2.	(Fisahn et al., 2005; Malkesman et al., 2010; Shaltiel et al., 2008)
Fmr1−/−	Fmr1 expression is disrupted in fragile-X.	Social deficits	Increase anxiety, and seizure susceptibility	mGluR5 activity increased. Reduced NMDA receptor expression. Disrupted AMPA receptor cycling. mGluR5 antagonist, and mGluR genetic reduction, reduce anxiety and seizure susceptibility.	(Eadie et al., 2010; Nakamoto et al., 2007; Westmark et al., 2009)
BTBR mouse		Social deficits, repetitive behavior		Disrupted metabolism of the endogenous glutamate antagonist kynurenic acid MPEP efficacy in reducing stereotypies.	(McFarlane et al., 2008; Moy et al., 2008; Silverman et al., 2010a)
Prenatal valproic acid exposure (VPA model)	Analogous to prenatal VPA in humans	Social deficits	Gamma-band EEG phenotypes associated with ASD	mGluR5 up-regulation MPEP efficacy Increased NMDA activity.	(Gandal et al., 2010; Rinaldi et al., 2007; Schneider and Przewlocki, 2005)
MECP2−/−	Rett syndrome models, MeCP2 expression reduced in ASD.	Social deficits, repetitive behavior		Decreased excitatory transmission. Reduced NMDA expression.	(Chen et al., 2001; Guy et al., 2001; Maliszewska-Cyna et al., 2010; Santos et al., 2007)
SHANK1−/−	Candidate gene	Social deficits	Increased anxiety	Excitatory synapse disruption. Reduced Excitatory transmission.	(Hung et al., 2008; Silverman et al., 2010b)
SHANK3−/+	Candidate gene	Social deficits		Excitatory synapse disruption. Reduced Excitatory transmission.	Bozdagi et al. (2010)
DLG-4−/− (PSD95 analogue)	Candidate gene	Social deficits	Increased anxiety	Excitatory synapse disruption. MPEP reduces anxiety.	Feyder et al. (2010)
Neurexin-1α−/−	Candidate gene	Repetitive behavior	Cognitive deficits	Reduced excitatory transmission	Etherton et al. (2009)
Neuroligin-1−/−	Candidate gene	Repetitive behavior	Cognitive deficits	Reduced NMDA/AMPA ratio	Blundell et al. (2010)

(Moy et al., 2008). Treatment with the mGluR5 antagonist MPEP successfully reversed the repetitive behaviors, but did not increase sociability. This study suggested a limited, but nevertheless promising, role for mGluR5 antagonists in treating core symptoms of ASD (Silverman et al., 2010a). Importantly, this work also indicated that MPEP and other mGluR antagonists are useful as a provisional test of predictive validity in models of ASD.

Similarly, in a mouse model where the homologue for human post-synaptic density protein 95 (PSD-95; mouse DLG-4) is disrupted, the mGluR5 antagonist MPEP was able to reduce signs of anxiety, but social deficits found in these mice were unaffected (Feyder et al., 2010). These mGluR5 findings may be directly related to rescuing specific synaptic abnormalities in the DLG-4 KO mice, as mGlur5, NMDA receptors, and ASD candidate genes in the SHANK family are functionally and physically associated with PSD-95 in the post-synaptic membrane (Guo et al., 2004; Tu et al., 1999).

Recent studies of MPEP in the Valproic acid (VPA) model of prenatally induced ASD further indicated a role for mGluR5. Mice prenatally exposed to VPA developed a number of core symptoms of ASD, paralleling earlier work in rats (Schneider and Przewlocki, 2005). Prenatal VPA exposure in mice also generates mice with intermediate EEG phenotypes of ASD (Gandal et al., 2010). The EEG phenotypes exhibited abnormal Gamma oscillations, which were reversed in the presence of MPEP (Gandal et al., 2010). Gamma abnormalities in response to auditory stimulation are an endophenotype of ASD (Rojas et al., 2008; Wilson et al., 2007). EEG abnormalities are an attractive endpoint, as they can be an intermediate endophenotype shared between models and patients, providing an acute readout of drug effects. Furthermore disrupted gamma-band activity signals a disruption of the circuit machinery generating gamma oscillations (Fries et al., 2007; Uhlhaas and Singer, 2010). Thus, these results provide a template for using EEG-intermediate phenotypes along with behavioral outcome measures for studying the role of glutamatergic agents in preclinical models of ASD.

4.3. NMDA receptors

In a number of models of ASD, NMDA receptors appear disrupted (Blundell et al., 2010; Eadie et al., 2010; Maliszewska-Cyna et al., 2010; Moy et al., 2008; Rinaldi et al., 2007). Clinically, there have been suggestions that the weak NMDA antagonists, amantadine, memantine and dextromethorphan, may have effectiveness in treating ASD (Chez et al., 2007; Erickson et al., 2007; King et al., 2001; Niederhofer, 2007). These clinical results would predict that NMDA hyperfunction has a role in ASD. NMDA receptor increases have also been found in a rat prenatal-VPA model (Rinaldi et al., 2007). In contrast, NMDA receptor levels are decreased in the FMRP1−/− mouse (Eadie et al., 2010), and in the MeCP2−/− mouse model of RTT (Maliszewska-Cyna et al., 2010). Targeting NMDA receptors in some models has been effective in normalizing behavior. In Neuregulin-1 KO mice, use of the NMDA coagonist D-cycloserine reduced potential signs of anxiety and repetitive behavior, indicating that increasing NMDA activity had a role to play in some ASD-associated symptoms (Blundell et al., 2010).

This lack of concurrence among models and the modest indications of NMDA hyperfunction in ASD suggest that NMDA differences may not be strongly linked to etiologies of ASD. Alternatively, these findings could be ascribed to a failure of the discussed models to replicate NMDA dysfunction as it occurs in ASD. Whatever the explanation in the context of hyperfunction, models of NMDA

hypofunction, which may have some validity for schizophrenia, can also have strong face validity for social deficits in ASD, and may be helpful in determining a role for NMDA in generating autistic phenotypes (Duncan et al., 2004; Moy et al., 2008; Ramsey, 2009).

4.4. AMPA receptors

The reduction of plasticity and post-synaptic excitatory potentials (EPSPs) in many models of ASD indicates downregulation of AMPA receptors in these models (as has been found in ASD (Purcell et al., 2001)). Long-term potentiation (LTP) and depression (LTD) are also often mediated by changes in AMPA receptor subunit expression in the post-synaptic membrane. These forms of synaptic plasticity are strongly associated with learning and memory, and disruption of these may underlie intellectual disabilities in ASD. AMPA receptors have been targeted in human patients using the nootrop piracetam, which works as an allosteric agonist at AMPA receptors, and has met with some potential success as an adjunct therapy (Akhondzadeh et al., 2008). It should be noted, however, that piracetam has many other potential targets in addition to AMPA receptors (Winblad, 2005). Ampakines, which also target AMPA channels, have been successfully used in treating some non-ASD-associated symptoms in the MeCP2−/− mouse models. In the case of ampakines, efficacy is attributed primarily to increased BDNF release (Lauterborn et al., 2000). Because targeting AMPA could provide for rescue of excitatory transmitter deficits, facilitation of LTP or LTD, recovery of cognitive deficits, and could also serve as an indirect means of increasing neurotrophin activity, there is a strong rationale for such work in models of ASD even without current clinical success.

5. Conclusion

5.1. Glutamate system dysfunction is a limited but common theme in models of ASD

Data from these ASD models indicate that excitatory transmission is often disrupted in models of ASD. Current work demonstrates that specific disruption of one candidate gene, or, in the case of VPA, models of induced ASD phenotypes, leads to disruption of other known candidate genes. Thus, these genes can be thought to form networks, whose interactions are important for normal synaptic function. Pharmacologically or genetically targeting mGluRs, GluR6, and NMDA, as well as a number of ASD-candidate genes, suggests that glutamatergic-associated changes within these networks may form mechanistic and behavioral subsets within a broader set of etiologies and phenotypes that co-occur in ASD. At the present juncture, this subset appears to link disrupted excitatory transmission to increased seizure susceptibility, anxiety, and the ASD-core symptom of repetitive behaviors and interests (Table 1). There is much less evidence that glutamatergic dysfunction mediates social deficits. Indeed, FMR1−/− mice demonstrated social deficits that are not mediated by mGluR5, suggesting a discrete non-glutamatergic mechanistic domain underlying social deficits in fragile-X. By contrast, neuroligin expression appears to interact with social deficits in the FMR1−/− model (Dahlhaus and El-Husseini, 2010), suggesting that FMR1 KO precipitates at least two distinct sets of impairments, only one of which is explained by the mGluR5 hypothesis.

The current work indicates that glutamate dysfunction, in the form of reduced excitatory transmission, dysfunction of NMDA mediated plasticity, and mGluR mediated signal transduction, has a role to play in the cognitive and behavioral pathologies of ASD. This hypothesis, delineating a role for disrupted glutamate signaling in ASD, needs to be more fully tested. To do so, studies similar to those described in the FMR1−/− mouse could be performed in a broad range of ASD models to determine if glutamate dysfunction mediates specific behaviors common to ASD models.

In transgenic and in models of ASD (including those that are possibly induced), the impact on glutamate receptors is primarily indirect. Thus the current models have a latent utility for exploring how different genetic risk factors interact to disrupt glutamate transmission, and how disrupted glutamate transmission may interact with other ASD-associated neuropathologies to generate the full range of ASD-associated behaviors. To directly determine the role of glutamate dysfunction on ASD-related behaviors glutamate receptors need to be specifically targeted for hyper- or hypofunction. Such models may be more tractable for preclinical development and tuning of therapeutics to treat glutamate receptor dysfunction in the autistic brain.

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