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Targeted treatments in autism and fragile X syndrome

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ABSTRACT

Autism is a neurodevelopmental disorder consisting of a constellation of symptoms that sometimes occur as part of a complex disorder characterized by impairments in social interaction, communication and behavioral domains. It is a highly disabling disorder and there is a need for treatment targeting the core symptoms. Although autism is accepted as highly heritable, there is no genetic cure at this time. Autism is shown to be linked to several genes and is a feature of some complex genetic disorders, including fragile X syndrome (FXS), fragile X premutation involvement, tuberous sclerosis and Rett syndrome. The term autism spectrum disorders (ASDs) covers autism, Asperger syndrome and pervasive developmental disorders (PDD-NOS) and the etiologies are heterogeneous. In recent years, targeted treatments have been developed for several disorders that have a known specific genetic cause leading to autism. Since there are significant molecular and neurobiological overlaps among disorders, targeted treatments developed for a specific disorder may be helpful in ASD of unknown etiology. Examples of this are two drug classes developed to treat FXS, Arbaclofen, a $GABA_B$ agonist, and mGluR5 antagonists, and both may be helpful in autism without FXS. The mGluR5 antagonists are also likely to have a benefit in the aging problems of fragile X premutation carriers, the fragile X-associated tremor ataxia syndrome (FXTAS) and the Parkinsonism that can occur in aging patients with fragile X syndrome. Targeted treatments in FXS which has a well known genetic etiology may lead to new targeted treatments in autism.

Contents

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1. Introduction

Autism spectrum disorders (ASDs) are common and occur in about 1% of the general population (Baron-Cohen et al., 2009). Although behavioral interventions at a young age are significantly helpful in children with ASD (Dawson et al., 2010), there are no pharmacological cures for these very impairing conditions that affect social interaction, communication, and behavioral domains. The etiology of autism is heterogeneous and may include genetic, environmental, and autoimmune etiologies (Levy, Mandell, & Schultz, 2009).

2. Neurobiology of autism

Autism is a highly genetic disorder and heritability is reported to be moderate to high (Hallmayer et al., 2011; Ronald & Hoekstra, 2011) and shared environmental factor are also important (Hallmayer et al., 2011). Research tells us that the genetics of autism is complex and caused by many different genetic mechanisms (Lo-Castro, Benvenuto, Galasso, Porfirio, & Curatolo, 2010). Some of the linkage and association studies have found candidate genes that contribute small effects on the autism phenotype (Veenstra-Vanderweele, Christian, & Cook, 2004). However, replication is not consistent across studies. On the other hand, recent studies suggest that rare genomic variation may explain a significant proportion of the genetic basis of ASD. One of the largest genome-wide association studies found a variant in the intergenic region between CDH 9 and CDH 10 (encoding cadherins 9 and 10) associated with ASDs in families (Wang, Zhang, & Ma, 2009). The finding of this study is important because its results implicate alterations in neuronal adhesion molecules in the pathogenesis of ASD, which could contribute to abnormal neuronal connectivity. Fassio, Patry, and Congia (2011) demonstrated that a mutation in the gene SYN1 (encoding the synaptic vesicle protein Synapsin 1) which predisposes to ASD and suggested that disturbances of synaptic homeostasis may underlies the pathogenesis of ASDs. Other studies have shown that mutations in synaptic proteins including neuroligins (Glessner, Wang, & Cai, 2009; Jamain et al., 2003) and neurexins (Arking et al., 2008; Kim, Kishikawa, & Higgins, 2008) are associated with autism. One of the well replicated finding about neurexins is association of CNTNAP2 (a gene named contactin associated proteinlike-2 which encodes Caspr2) and autism. This association was documented in several studies in various populations (Alarcón et al., 2008; Bakkaloglu et al., 2008; Li et al., 2010). Copy-number variations (CNVs) are consistently found associated with autism in the large family studies (Levy, Mandell, & Schultz, 2009). Although new strategies to identify common genetic risk variants are being applied currently, there is no single model that explains all of the phenotypic variation in cases with autism (Buxbaum, 2009). In fact, genetic heterogeneity data strongly suggest that there is not any common genetic risk variant. In a recent study, a large number of investigators presented a new approach called homozygous haplotype mapping, which aims to detect homozygous segments of identical haplotype structure that are shared at significantly higher frequency among individuals with ASD compared to parental controls. Using this strategy authors are able to identify many new ASD candidate genes and replicate some older ones (Casey et al., 2012), and they suggested this approach as a promising development to evaluate genome wide association data.

Although available data suggest that a large proportion of ASD cannot be explained by single-gene models, these models represent a means of understanding the underlying neurobiology of autism (Abrahams & Geschwind, 2008) and they include fragile X syndrome (FXS) (Hatton et al., 2006), Tuberous Sclerosis (Wiznitzer, 2004), Rett syndrome (Young et al., 2008) and some other less known chromosomal abnormalities (Lo-Castro, Benvenuto, Galasso, Porfirio, & Curatolo, 2010). Functions of *FMR1*, *MECP2* and some of the neural adhesion molecules such as neuroligins/neurexins suggest synaptic dysfunction in autism pathogenesis. Overall, genetic and neurobiological evidence demonstrate that there are similarities across disorders that are associated with autism including GABA and glutamate imbalances (Belmonte & Bourgeron, 2006), synaptic maturation and plasticity deficits (De Rubeis & Bagni, 2011; Levy, Mandell, & Schultz, 2009) and mitochondrial malfunction (Giulivi et al., 2010).

Neurotransmitters including GABA, glutamate and serotonin are important in functions of synaptic interactions and in cortical development (Manent & Represa, 2007; Pardo & Eberhart, 2007). Specific GABA and glutamate receptors have a role in neuronal migration, inhibition and synaptic plasticity including long term depression (LTD) and long term potentiation (LTP). Plasma levels of glutamate and glutamine were found to be high in high-functioning children with autism (Shimmura et al., 2011). The authors suggested that the plasma levels of glutamate and glutamine could be early markers of glutamatergic dysfunction leading to an autism pathogenesis. In animal models it was shown that GABAergic dysfunction in early development lead to excitatory/inhibitory imbalances in neural circuits and may account for some of the behavioral symptoms of ASDs (Pizzarelli & Cherubini, 2011).

The role of serotonin in autism is also widely explored and abnormalities documented in PET/SPECT studies and genetic studies found a relationship with serotonin related genes (Pardo & Eberhart, 2007). Serotonin levels were found to be low in the frontal region of the brain in children with autism under age 5 with alpha [11C] methyl-L-tryptophan and PET scans (Chugani et al., 1999). Although some studies have demonstrated an improvement in autism features following treatment