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Research report

Novel treatments in autism spectrum disorders: From synaptic dysfunction to experimental therapeutics

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HIGHLIGHTS

- New pathways in neurobiology of ASD.
- Single gene disorders and ASD.
- New treatments in ASD.

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ABSTRACT

Recent discoveries and advances in genetics and neuroscience have provided deeper understanding of the complex neurobiology of ASD. The development of novel treatments is strictly dependent on these findings in order to design new strategies in the pharmacotherapy of ASD. At this time, therapeutics are limited to treating associated core, symptoms. Studies of single gene disorders, such as Phelan-McDermid syndrome, Fragile X and Tuberous Sclerosis, might be of significant help since the neurobiology of these disorders is clearer and clinical trials are already underway for these conditions. The pathogenesis paradigm shift of ASD towards synaptic abnormalities has led to current research of the pathways to disease, which involves multiple dynamic systems. Interest in oxytocin is growing as it has been recognized to be implicated in social development and affiliative behaviours. In the future, progress is expected in possible new options for therapeutics in ASD. Children and adolescents with ASD and their families can provide vital information about their experiences with new treatments, which should be a priority for future research.

Progress in neuroscience and genetics is continuously providing new clues to the complex neurobiology of autism spectrum disorders (ASD) and these advances are of great value in supporting the development of novel treatments. At present, there is no cure for the core symptoms of ASD and there is no modifying treatment for the basic disturbances that characterize this wide and heterogeneous group of developmental disorders. Only specific symptoms, those under the broad definition of irritability, have been demonstrated to decrease with current pharmacological treatments [1]. Continued efforts in understanding the neurobiological and genetic underpinnings of ASD are crucial for progress in therapeutics. Although it is widely recognized that the genetic risk of ASD is high, as much as 60–90% [2,3], the genetic causes remain unknown in the great majority of cases. Considering copy number variants (CNVs) and single gene disorders associated to ASD, the genetic yield is less than 15% of individuals with ASD [4,5]. Recent research has highlighted that the discovery of new therapeutics for ASD can be derived from what has been learned from related single gene disorders. Previously, there was a frequent reluctance to deal with rare genetic conditions associated with ASD, compared to the great attention paid to the large proportion of individuals, around 90%, affected by idiopathic ASD, e.g. of unknown genetic cause. So far, Rett Syndrome, Fragile X and Tuberous Sclerosis, which fall in the ASD spectrum, have provided paradigmatic models for targeted treatments [5]. As new information has become available regarding the neurobiology and neurogenetics of these conditions, the forefront of research has developed in human clinical trials, following and in parallel with preclinical and animal studies, all of which have opened new avenues for research and for the treatment of ASD [6,7]. One of the main questions regarding these novel approaches is whether these therapeutics will also be useful for the larger population of individuals with idiopathic ASD. It should be clearly noted that at present there is a wide range of behavioural interventions, treatments that are safe and effective for improving cognitive and language abilities and adaptive behaviour in children with ASD [8]. However, children and adolescents with ASD and associated

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behavioural disorders can receive additional benefit from the use of pharmacotherapy.

1. Pharmacotherapy of ASD for associated behavioural disorders

Currently, there are well established treatments with medications that address almost exclusively the symptoms associated with ASD known under the umbrella term of irritability i.e. tantrums, aggression, self injury and hyperactivity [9]. It is worthwhile to emphasize that the nuclear social and communicative abnormalities of ASD are scarcely, if not at all, modified by current pharmacotherapy and this remains a priority in the field. Two second generation antipsychotics, also known as atypical, risperidone and more recently aripripazole [10–12], have been approved for symptomatic treatment of ASD. Both have been demonstrated to be effective in reducing maladaptive behaviours, e.g. irritability, that so often interfere with daily living activities and educational approaches. Unwanted side effects are also relatively frequent with second generation antipsychotics and caution is recommended in their administration. Although antipsychotics are not expected to modify the core aspects of ASD, it should be noted that a general improvement in behavioural symptoms is expected. Additional gains in adaptive behaviours and compliance with educational programmes further supports the choice of administering these medications for these aims.

2. Pharmacotherapy of core symptoms of ASD

The pharmacological treatment of the nuclear social impairment of ASD is still elusive and it calls for intense research efforts. The specific core abnormalities affecting social reciprocity, socio and emotional interest and engagement are poorly, if not at all, modified by current pharmacological treatment and behavioural interventions are the mainstay of treatment from early childhood up to adolescence [1,9]. However, there is a great need for the development of medications that can help reduce the core symptoms of ASD, including those for attenuating repetitive behaviours and restricted interests that are a major flaw in the achievement of developmental milestones, executive functions and symbolic play in children with ASD. The broad individual differences found among patients with ASD in their symptoms and overall needs were some of the major difficulties in developing effective treatments. The major questions are how to best identify the individuals who will be most responsive to a specific treatment, and how to measure the treatment effect in such heterogeneous conditions, e.g. planning an adequate set of outcome measures that might fit the variability in core symptoms in ASD [6]. To date, a number of outcome measures employed in clinical trials have been identified, but these need further refinement and revisions in light of the new targeted treatments. Increasing knowledge of the abnormal neurobiological pathways of ASD is ongoing and new outcome measures should be sorted out accordingly. The outcome measures used now, in fact, were tailored only on behavioural measures and not on the biological parameters that are now under intense investigation.

3. Synaptic abnormalities, single gene disorders and ASD (Table 1)

A growing body of data is becoming available which supports the conceptualization of ASDs as a collection of multiple genetic etiologies that disrupt the development and function of brain circuits mediating social cognition and language. The large number of ASD related genes identified in several studies could have common final pathways that could possibly be targeted in drug treatments. Copy number variations or mutations in any single gene within a pathway may determine a specific phenotype, and it is becoming clearer that a number of genes related to ASD are involved in the same pathway(s) that might be considered as putative target(s) for treatment [6,13]. The recent change in paradigms on neural abnormalities in ASD has opened new avenues in the search for novel treatment. Preclinical studies of ASD susceptibility genes have the potential to shed light on the disrupted signalling pathway that could become the specific target for therapeutic interventions [14,15]. The current paradigm shift towards synaptic abnormalities vs neuronal wiring in permanent alterations in ASD was formulated on the basis of recent findings in animal models and it has important implications. Rather than an ASD model based on a stable abnormal neuronal network nested in early brain development, abnormalities of synaptic signalling and plasticity have become the focus of interventions likely to be modified by targeted therapeutics.

Table 1
Single gene disorders, ASD and experimental therapeutics.

Syndrome	Gene	Clinical characteristics	Study drug
Rett syndrome	MECP2	Regression, head circumference deceleration, hand apraxia, stereotipies, absence of language, epilepsy	IGF-1
22q13 deletion syndrome	SHANK3	Developmental delay, hypotonia, no language, seizures	IGF-1
Fragile X	FMR1	Macrochephaly, macroorchidism, language impairment, social, hyperactivity	Arbaclofen AFQ056 RO4917523
Tuberous sclerosis	TSC1/2	Language and cognitive impairment, hyperactivity, epilepsy	Everolimus

3.1. Synaptic abnormalities in ASD

Several synaptic abnormalities in ASD have been described. Dendritic spines are of primary importance for synaptic plasticity and function, and they are responsible for most excitatory glutamatergic transmission [16]. Alterations in dendritic spine morphology and density have been documented and they are important micro structural modifications that are implicated in abnormal synaptic transmission in ASD [17]. Synaptic modifications have been demonstrated in animal models and in post mortem studies from subjects with FXS, TSC and Rett syndrome, all genetic conditions frequently presenting with ASD features [18], Table 1. However, since spine abnormalities are also commonly found in mental retardation, the specificity of spine density increases is unclear and it is hypothesized that they are more related to mental retardation in a broader sense than in representing a specific finding of ASD. The only post mortem study performed as yet in humans demonstrated changes in spine morphology in the brain of a subject with ASD. Spine densities were negatively correlated with cognitive performance in subjects with ASD [19]. Thus, abnormal dendritic spines maturation has become a therapeutic target in ASD and growth factors have been introduced in therapeutics to enhance impaired maturation of synapses.

3.2. Single gene disorders and ASD

Since each of the rare CNVs associated with autism has been identified in a very small number of individuals with ASD, a relatively large number of genes are thought to be involved in the pathogenesis, and a large phenotypic variability expression further complicates the identification of the genetic abnormality in ASD [7].