Review

Future Directions in Autism Treatment

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Autism spectrum disorder (ASD) affects up to 1 in 88 American children and the cause is largely unknown. The latest research showed encouraging results on using metabotropic glutamate receptor 5 (mGluR5) blockers in mice models of autism. It raised hope for innovative pharmacological intervention for this neurodevelopmental disorder and generated guarded excitement in the autism community. Further basic research is needed to understand the roles of glutamate and other neurotransmitters, such as GABA and oxytocin, in the pathophysiology of ASD. In the meantime, multicenter randomized controlled clinical trials are potentially on the horizon to curb or reverse the core symptoms of autism.
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INTRODUCTION

Autism spectrum disorder (ASD) is a group of neurodevelopment disorder characterized by impaired social reciprocity and interaction, abnormal communicative intent, and repetitive, stereotyped patterns of behavior, interests and activities with onset before the age of three.[1,2] It is estimated that up to 1 in 88 U.S. children has ASD, according to the U.S. Centers for Disease Control and Prevention.[3]

The etiology of ASD remains ill-defined with many competing hypotheses. Physicians have yet to find clinically effective treatment, much less a cure. Many medications have been developed that provide varying degrees of clinical success to remedy specific symptoms, but none of them have targeted the basic underlying pathological changes. Early behavioral interventions can often reduce symptoms associated with the disorder, lessen disruptive behavior, provide some degree of independence, and improve the overall quality of life for children with ASD. Many children with the disorder can learn and develop with appropriate treatment and education. As indicated by Dr. Rogers, early intervention programs are indeed beneficial for children with autism, however the general outcomes could vary dramatically.[4] Some cutting-edge medical advances have been attempted to treat autistic patients, such as stem cell therapy,[5,6] and Functional MRI Guided Transcranial Magnetic Stimulation.[7,8] These are promising yet are premature for routine clinical use; In certain autistic patients, treatment of medical comorbidities lead to symptoms improvement.[9,10]

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Genetic causes of autism are well recognized and documented by studies in recent years. Researchers have revealed that certain genes involved with autism regulate the formation of brain synapses throughout childhood, and even into adulthood.[11,12,13] This has led many to conclude that the core symptoms of disorders such as autism, Fragile X Syndrome (FXS), and Rett syndrome, cannot be cured or even treated with medication, since the underlying abnormalities in the brain are determined by genetic codes during fetal and neonatal development, despite the fact that environmental factors and their interactions with genes also play crucial roles.[14]

Many active therapies have been developed over the years to challenge the view that autism is untreatable because it is genetically determined. The current therapies, however, have fallen far short of expectations.[15,16] The slow and disappointing progress in autism treatment could be attributed to the limited knowledge of its pathophysiology. Without a correct and clear understanding of the disease, trying various therapies is like throwing darts in the dark.[17]

GLUTAMATE AND AUTISM

Neurotransmitters and its role in neuropathological disorders have been studied for many years.[18] Glutamate is the primary excitatory neurotransmitter in the mammalian brain activating brain cells, or neurons. Glutamate exerts its effect via metabotropic and ionotropic glutamate receptors. Ionotropic glutamate receptors form ion channel pores that open when bound by glutamate agonists. There are three subtypes of ionotropic glutamate receptors, AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate), NMDA (N-Methyl-D-Aspartate) and kainate. Metabotropic glutamate receptors (mGluR) are coupled to G proteins to activate

second messengers. There are 8 subtypes of mGluR, numbered from 1 to 8.

Abnormally high glutamate level leads to over excitation of neurons or even neuronal death. Therefore a glutamate imbalance is often considered as a potential culprit for many neurological disorders. Excessive glutamate can even function as a neurotoxin in certain circumstances.[19] Disturbances in glutamate-mediated neurotransmission have been demonstrated in multiple neuropsychiatric disorders such as schizophrenia and autism.[20] It has been hypothesized that high activity of glutamate is the core substrate that causes autism. Therefore, compounds that can reduce the activity of glutamate hold promise in reversing the symptoms of autism.[21] Indeed, off-label use of Memantine, a noncompetitive antagonist of the NMDA receptor, significantly improved language function, social behavior, and self-stimulatory behaviors in some autistic patients.

Neurodevelopmental disorders such as Autism spectrum disorders (ASD), Fragile X Syndrome (FXS), and even Rett syndrome share overlapping behavioral characteristics, implying they may have similar core neuropathogenesis. In particular, delayed synaptic maturation, abnormal synaptic structure and/or function and alterations in intracellular signaling pathways have been linked to the pathogenesis of FXS and ASD.[17] Aberrations in ionotropic GABA (A) receptor and the G-protein coupled metabotropic glutamate and GABA(B) transmitter systems are also linked to both disorders and these receptors are currently at the forefront of preclinical and clinical research into treatments for both autism and FXS.[17,21] Animal models of FXS have also been considered a preliminary model for ASD, and their overlapping biochemical characteristics may reveal new directions for the potential development of pharmacological therapies that might prove useful in the treatment of both FXS and ASD.

FXS, also known as Martin-Bell Syndrome, is known to be caused by a specific mutation of Fmr1 (fragile X mental retardation 1) gene, resulting in constant activation of metabotropic glutamate receptor 5(mGluR5). The mGlu5 receptors are often localized around NMDA receptors and the two glutamate receptor subtypes for a strong functional relationship. In addition, mGlu5 also serves as auto receptor to regulate the release of glutamate. Therefore, pharmacological mGlu5 inhibition is naturally a choice for FXS treatment. In April 2012, scientists from Roche and Massachusetts Institute of Technology reported in Neuron [22] that treatment of Fmr1 knockout mice at 4-5 weeks (the equivalent of older children or young adults in human) with a new mouse mGlu5 inhibitor CTEP (also known as RO4956371), reversed FXS phenotype. Strikingly, a single dose of CTEP treatment corrected elevated auditory induced seizures. Chronic treatment rescued almost all abnormalities in the knockout mice such as cognitive deficits, auditory hypersensitivity, and aberrant dendritic spine density.

That same month, another team of scientists from Pfizer and the National Institute of Mental Health (NIMH) published a vigorous study in Science Translational Medicine that tested another mGluR5 antagonist, GRN-529, in two different mouse models of autism.[23] The two inbred strains of mice were called BTBR and C58/J, respectively. BTBR mice had shown all three core characteristics of autism, including unusual social interactions, impaired communication and repetitive self-grooming. C58/J mice had a tendency to jump repeatedly, a trait that mimics the repetitive behaviors seen in people with autism. A single dose of GRN-529 reduced the frequency of self-grooming during a ten minute interval in BTBR mice, compare to those that received a placebo. It also reduced repetitive jumping in C58/J mice. More interestingly, GRN-529 also improved social interactions in BTBR mice, although their communication was still not typical. In one assay for social approach to an unfamiliar mouse, BTBR mice treated with GRN-529 were more likely to investigate a stranger mouse instead of an object. In another assay to test for social interactions between freely moving pairs of mice, a GRN-529 treated mouse was more likely to touch noses with its cage mate. In addition, it is worth pointing out that the researchers repeated their findings in two laboratories using several separate groups of mice.

GLUTAMATE AND GRN-529

Although the two studies are only animal studies, it is the first time that the scientists successfully applied our understanding of neurochemical changes in autism to treat such a complicated and heterogeneous disorder. Previously, no core symptoms of autism was even targeted in preclinical research.[24] Without doubt, new research that focuses on developing medicines for core symptoms of autism is gaining momentum.

The ability of GRN-529 to instantly reduce repetitive behavior and partially reverse the lack of sociability in a mouse model of autism provides a strong rationale to further test mGluR5 receptors in additional animal models of autism. For example, a deletion of a gene called Shank3, which encodes a protein that forms a cluster with glutamate receptors and helps stabilizing synaptic connections between neurons, produces the same three core symptoms of autism. It would be interesting to administer GRN-529 to Shank3 mutant or knockout mice to see if similar beneficial results can be obtained.

The recent findings [22,23] will certainly raise interest to further exploring the molecular mechanisms involving the mGluR5 receptor and open more avenues for research. GRN-529 alleviated or reversed some core symptoms in mice, but not completely. For instance, the mice still didn't communicate normally. If inhibiting glutamate pathway proves to be an effective intervention, then a wide range of compounds should be studied to select the most effective candidate. In addition, for clinical use, it is very likely that we need to develop a new drug that has optimal pharmacokinetics in human body.

The recent advance offers additional evidence to link deficient glutamatergic neurotransmission and autism, but more importantly it provides hope that a phenotype caused by

genetic changes can be reversed well after the early development period. These findings imply that an effective drug treatment might be available not only for autistic children, but for autistic adults as well.

This recent breakthrough is an exciting hint that the mGluR5 inhibition may have broad applications in both FXA and ASD. Still, it is too early to speculate as to whether the pathophysiology of ASD can be reversed by small molecules such as mGlu5 antagonists in human beings.[17,24] Many successful animal studies don't translate into effective clinical treatments. Although mice are often used to model human diseases in medication development, mice and human beings are different in many ways, especially in terms of parameters for social interaction. For example, mice don't have to learn much throughout their lifetime to engage in their daily activities, whereas in humans it takes years of learning in order to function well in a typical social setting. In addition, we don't know how well interventions that normalize social interest at a defined time and setting will work over the long term when social interactions are dynamic and appropriate responses vary.

Multiple clinical trials for FXS are already under way by Novartis, Seaside Therapeutics and Roche to test different compounds that inhibit glutamate signaling pathway.[24] Of course we hope these medications will help not only FXS victims, but those with ASD as well. Given the recent promising results in animal studies, it is possible that similar clinical trials will be on the horizon to treat ASD. If trials show drugs are effective, a major question would be whether children should receive the drugs when diagnosed or if adults could also benefit from them. Of course, it is too early to make any confident predictions. But our understanding of autism is progressing rapidly and we have reasons to expect more breakthroughs in the years to come.

It is also worth pointing out that many cases of autism are likely to be involved more than excessive glutamate signaling and it is reasonable to speculate that drugs targeting other neurotransmitters or their receptors, such as GABAergic system, may very well be effective in treating autism.

OXYTOCIN

Oxytocin (Oxt) is a mammalian hormone that acts primarily as a neuromodulator in the brain. It plays a key role in regulating prosocial behavior and social cognition in animals and humans. It is been best known for its roles in sexual reproduction, in particular during and after childbirth. It is released in large amounts after distension of the cervix and uterus during labor, facilitating birth, and after stimulation of the nipples, facilitating breastfeeding.[25, 26]

Only recently years scientists have started to study oxytocin in areas such as orgasm, social recognition, pair bonding, anxiety, and maternal behaviors. With its role in sexual orgasm, it is referred to as the "love hormone".[27] It is further revealed that the body's inability to secrete oxytocin is likely associated with sociopathy, psychopathy, narcissism, and general manipulativeness.[26, 27]

As ASD patients have deficits in social interaction, some researchers have explored behavioral phenotypes in mice with different types of oxytocin deficiency.[28] Oxytocin ligand or receptor knockout mice, as well as mice with deficiency in oxytocin exocytosis, all demonstrate autistic like behavior.

Human studies also found association between oxytocin receptor polymorphisms and ASD.[29] In addition, oxytocin treatment could fully reverse social and behavioral deficiencies in oxytocin receptor knockout mice.[30]

Oxytocin cannot easily cross blood brain barrier and it is susceptible to enzymatic breakdown, but intranasal administration has been found to be an effective route in clinical use.[31] In one study, Elissar Andari et al reported that in a simulated video ball game, 13 patients with high functioning autism became more likely to interact with and trust socially responsive characters after oxytocin administration. Moreover, oxytocin also made patients pay more attention to human faces and the region around eyes.[32] In another recent study, Australian researchers tested 16 adolescent patients with ASD in a double blinded experiment. They found a single dose of oxytocin administration improved emotion understanding in ASD patients compare to the performance of those who received placebo.[33] A clinical phase 2 trial of intranasal oxytocin treatment of autism has just been concluded and we expect results to be published soon.[34]

SUMMARY

Neurotransmitters such as glutamate have long been suspected to play a role in ASD. Glutamate receptor antagonists have great potential in curbing or reversing the core symptoms of ASD. In addition, neuromodulators such as oxytocin may be applied to improve social functions of autistic patients and early results using intranasal oxytocin are promising.

CONFLICT OF INTEREST
None

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