Narrative review

Glutamate's role in symptom control of autism spectrum disorder

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Abstract
Autism spectrum disorder is a complex and persistent condition that has received increasing attention through the recent decades. Numerous research studies have highlighted the role of the neurotransmitter glutamate in this disorder, suggesting that alterations in its function could be significant in the development of the disorder's symptoms. Literature research was conducted in the PubMed, MEDLINE, Google Scholar, Scielo, and PsycARTICLES databases from 2019 to 2024, original and review articles in English and Spanish were selected to evidence the influence of neurochemical imbalance on the development of autism symptoms. The findings proved a relationship between the neurochemical imbalance of glutamate and some symptoms of ASD, suggesting that the receptors of this neurotransmitter could be involved as therapeutic targets, positive developments were observed in verbal intellectual quotient and improvement in social responsiveness after treatment with allosteric modulators of glutamate receptors.

Keywords
Autism Spectrum Disorder, Glutamate Receptors, Neurodevelopmental Disorders.

Resumen
El trastorno del espectro autista es una condición compleja y persistente que ha recibido cada vez más atención en las últimas décadas. Diversas investigaciones han resaltado el papel del neurotransmisor glutamato en este trastorno, sugiriendo que las alteraciones en su funcionamiento podrían desempeñar un papel clave en el desarrollo de sus síntomas. Para la elaboración de esta revisión narrativa, se realizó una búsqueda bibliográfica en las bases de datos PubMed, MEDLINE, Google Académico, SciELO y PsycARTICLES de los años 2019 a 2024, se seleccionaron artículos originales y de revisión en inglés y español, con el objetivo de evidenciar la influencia del desequilibrio neuroquímico en el desarrollo del trastorno del espectro autista. Se demuestra la existencia de una relación entre el desequilibrio neuroquímico del glutamato y algunos síntomas del trastorno del espectro autista, que permite involucrar los receptores de dicho neurotransmisor como objetivos terapéuticos; se ha observado un desarrollo positivo en el coeficiente intelectual verbal y una mejora en la capacidad de respuesta social después del tratamiento con moduladores alostéricos de los receptores de glutamato.

Palabras clave
Trastorno del Espectro Autista, Receptores de Glutamato, Trastornos del Neurodesarrollo.

Introduction

Autism spectrum disorder (ASD) is a set of complex and persistent neurodevelopmental disorders characterized by two main domains: social interaction and communication and restrictive and repetitive behaviors. It is important to mention that symptoms must be present from the early stages of development and cause clinically significant social and occupational impairments.[i]

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This spectrum encompasses a diversity of disorders that share characteristics such as difficulties in social communication, restricted behaviors and the display of repetitive behaviors.[ii] In recent decades, the incidence of ASD has increased globally, affecting both boys and girls, and this could be due to the increase in diagnostic tools for this disorder. The World Health Organization (WHO) estimates that one in every 100 children is diagnosed with ASD in the United States; by 2016, one in every 36 children was diagnosed with this disorder.[iii] ASD poses economic and social challenges to the patients, with maintenance and subsistence costs exceeding $60 000 per year in the United States. In addition, only 15-20 % of adults with ASD are employed.[iv]

Currently, the origin of ASD is not fully understood. However, it is recognized as a complex condition in which genetic, neurobiological, and environmental factors interact.[v] An example of this is mutations in genes responsible for encoding receptors for various neurotransmitters, which are compromised in ASD and thus contribute to some of its distinctive features, such as glutamate, a crucial neurotransmitter with inhibitory effects that are involved in ASD.[vi] There are several studies, such as those by Hardan *et al.*, Schiller *et al.*, or Soorya *et al.*, which have demonstrated the efficacy of drugs acting on the regulation of glutamate concentrations at the brain level to provide a new therapeutic tool for symptom control in ASD patients, which is of utmost importance due to the limited number of treatments available.[vii-ix] Preclinical and clinical studies have corroborated the efficacy of glutamate receptor allosteric modulators in regulating neuronal excitability and synaptic conduction, which decreases the behavioral and cognitive effects of ASD.[x]

A literature search of databases was conducted for this narrative review, including PubMed, MEDLINE, Google Scholar, Scielo, and PsycARTICLES. Keywords such as autism, "intervention", "glutamate", "receptors" and "therapies", both in Spanish and English, were used to broaden the search results. Fifty scientific articles were selected according to the inclusion and exclusion criteria selected from the publications obtained using the search filters. One of the inclusion criteria for selecting studies was that they had to be published between 2019 and 2024. Additionally, only experimental and descriptive studies, available in Spanish or English, were considered. Those with a lack of adequate documentation for diagnostic confirmation by standardized tools were excluded in order to evidence the influence of neurochemical imbalance with the development of symptoms of autism spectrum disorder.

Discussion

General aspects of autism spectrum disorder and glutamate receptors

ASD is a pervasive neurodevelopmental disorder that can hinder skill acquisition. The WHO defines it as difficulties in social skills and communication with the environment, as well as inflexible or repetitive behaviors, unusual interests, and variations in the perception of sensory stimuli. Its development is influenced by a variety of factors, including environmental, genetic, and prenatal aspects.[xi]

It is characterized by a multifactorial etiology, although a precise cause triggering the associated neurological changes has not yet been identified. However, an alteration in brain connectivity, both in function and structure, has been observed.[xii] This phenomenon can occur in individuals of various races, ethnicities, socioeconomic backgrounds, and gender. However, it is more prevalent in boys than in girls, with a ratio of approximately two to one.[xiii]

Clinical symptoms are typically identified during the second year of life, although they may appear earlier in some cases. They can manifest in different ways: in some cases, a child follows a typical development and then experiences stagnation; in other cases, the opposite may occur, where children who have followed a normal pattern experience regression in language, communication, and loss of previously acquired skills.[xiv]

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) categorizes ASD into three levels of severity, which include symptoms associated with social communication, repetitive and restricted behaviors. The first level implies a need for support, the second level a substantial need for support, and the third level denotes a very substantial need for support.[i,xv]

Several factors influence the biological origin of ASD at the brain level. Among them, alterations in the neuronal pathways stand out, particularly the imbalance between the glutamatergic (excitatory) and GABAergic (inhibitory) pathways, as well as dysfunctions in the cholinergic pathway, synaptic plasticity, and oxidative stress processes. Similarly, several comorbid disorders have been reported in ASD, such as anxiety disorder, sensory processing,

sleep, attention deficit, oppositional defiant disorder, intellectual disability, obsessive-compulsive disorder, etc.[xvi]

Glutamate, a key neurotransmitter in the central nervous system (CNS), plays a crucial role in the normal transmission between neurons, thereby facilitating communication between them. It also plays a crucial role in the plastic changes of the CNS during development, as well as in learning and memory processes. Its dysfunction has been associated with several diseases, including Alzheimer's disease, Parkinson's disease, and certain forms of epilepsy, and is involved in the treatment of ASD.[xvii]

Advances in genetic technology and diagnostic testing have made it possible to identify specific causes of ASD in approximately 40 % of patients with access to specialized genetic services. These studies focus on the detection of genetic syndromes, molecular and cytogenetic alterations, as well as metabolic disorders. For example, mitochondrial disorders may affect up to 20 % of people with ASD, along with the possible involvement of other metabolic disorders.[xviii]

Glutamate and its receptors in the development of autism

Brain development is a highly complex process involving numerous events such as synaptogenesis, axonal and dendritic arborization, neuronal migration, and synaptic plasticity, among others. These processes aim to establish the full functionality of the brain.[xix] However, sometimes, alterations at the cellular, biochemical, and structural levels may occur during neonatal development. Among the possible neurobiological causes of autism, the presence of abnormalities in the formation and function of synapses has been suggested.[xx]

Glutamate, which is a substance used as a substrate in protein synthesis, is the most prevalent excitatory neurotransmitter in the brain, used in approximately two-thirds of synapses. Glutamatergic transmission plays a crucial role in regulating motor, sensory, and cognitive systems and is involved in fundamental processes such as synaptic plasticity, adult neurogenesis, and neurodegeneration.[xxi]

During brain development, glutamate receptors change their distribution and molecular characteristics, rendering the brain more susceptible to variations in glutamate neurotransmission during growth. For this reason, the role of neurotransmitters and their receptors during the early stages of development is of paramount importance.[xxii]

During the 1990s, early studies focusing on plasma glutamate levels revealed a significant increase in these levels in children with ASD compared to controls. Similarly, more recent research has demonstrated a decrease in plasma glutamine levels, which are directly related to glutamate levels.[xxiii]This same glutamate-glutamine relationship has been observed in relatives of patients with ASD, as well as when comparing patients with autism with healthy individuals. These investigations clearly underline the implication of glutamate concentration in the development of this disorder.[xxiv]

The imbalance between GABA, the main inhibitory neurotransmitter, and glutamate, the main excitatory neurotransmitter, is an area of interest in autism spectrum disorder research because it has been suggested that this imbalance may contribute to the symptoms observed in autism spectrum disorder.[xxv] On the other hand, it has been proposed that there may be hyperactivity of the glutamatergic system or under activity of the GABAergic system in certain areas of the brain of individuals with ASD, which may contribute to increased neuronal excitability, problems in the modulation of sensory processing, and difficulties in the integration of sensory information, which are common features of autism.[xxvi]

In a study by Ajram *et al.*, a reduced GABA/glutamate ratio was found in the frontal lobe of children with autism, in the occipital lobe of adolescents with high-functioning ASD, and the prefrontal cortex of adults with this disorder.[xxvii] On the other hand, a 2020 investigation in New Jersey by Bhandari *et al.*, observed increased GABA levels in the visual cortex, decreased GABA levels in the sensory-motor cortex, and a decreased GABA/creatinine ratio in the anterior cingulate cortex in children with ASD compared to control individuals. These findings underscore the importance of maintaining a balance between excitatory and inhibitory stimuli in the development of autism.[xxviii]

It is worth mentioning that excitatory neurotransmitter signaling, mediated by glutamate receptors, regulates cognitive functions such as memory and learning, which are often compromised in autism.[xxix] Furthermore, being found throughout the central nervous system, glutamate plays a key role in brain development by influencing processes such as neuronal migration, differentiation, survival, and synapse formation.[xxx] However, at high concentrations, glutamate can act as a potent neurotoxin that causes cell death, which could be part of the pathophysiology of certain neurological disorders, including ASD. Although glutamate has

difficulty crossing the blood-brain barrier, its plasma and CNS levels are closely related.[xxxi]

Children with ASD have been found to have significantly higher plasma glutamate concentrations compared to healthy controls and controls with intellectual disability, which has been corroborated in post-mortem studies revealing anatomical changes in regions such as the cerebellum and hippocampus.[xxxii] These findings support the idea that alterations in glutamate signaling may play an important role in the pathophysiology of autism. However, more research is needed to understand from a mechanistic perspective the basis of the origin of ASD.

It is critical to recognize that autism is a complex and multifactorial disorder and that the relationship between imbalance in GABA and glutamate neurotransmission with ASD symptoms is not yet fully understood. Nevertheless, this area of research remains highly relevant and may offer new insights into the underlying biology of ASD and possible therapeutic approaches.[xxxiii]

Moreover, it is important to mention that metabotropic glutamate receptors (mGluRs) are a type of G-protein-coupled receptors that are activated by glutamate action in the CNS. In general, they are responsible for modulating synaptic efficiency and regulating the precision of neurotransmission. Among the eight subtypes, mGluR1 and mGluR5 belong to the group 1 (Gp1) family and are associated with various neurological disorders, including Alzheimer's disease, autism, and Parkinson's disease.[xxiv] Group1 mGluRs are distributed differently throughout the CNS. While mGluR1 is mainly found in the hippocampus, cerebellum, and substantia nigra, mGluR5 is expressed in the hippocampus, amygdala, olfactory bulb, striatum, nucleus accumbens, septum, and dorsal horn.[xxxv]

In addition, Gp1 mGluRs can also be affected by the allosteric binding of certain modulators, such as positive allosteric modulators (PAMs) and negative allosteric modulators (NAMs), which cause sensitization or desensitization of these receptors. PAMs and NAMs indirectly regulate glutamate transmission and are therefore used in clinical trials targeting related CNS disorders.[xxxvi]

While the exact pathogenic mechanism of ASD remains elusive, studies in mouse models of ASD and patients suggest the involvement of Gp1 mGluRs in the disorder[xxxvii] CFMTI, a selective mGluR1 antagonist, ameliorates MK-801-induced social interaction deficits in rodents, suggesting the therapeutic potential of mGluR1 antagonists in addressing pathological social interactions.[xxxviii] However, research on mGluR1 has focused primarily on cognitive rather than emotional and behavioral dysfunctions in rodent models of ASD. Although mGluR1 antagonists have shown efficacy in schizophrenia models, their application in ASD has not been as extensively studied. Research in this area is limited, and further studies are required to determine the efficacy and safety of these treatments in the management of ASD.[xxxix]

ASD is influenced by genetic and environmental factors, suggesting that treatment with Gp1 mGluRs antagonists may address individual symptoms rather than the disorder as a whole. Therefore, a combination treatment of multiple therapies may be necessary to intervene in the progression of ASD effectively.

Glutamate receptor antagonists and symptom control in patients with autism

Treatment for ASD is carried out in several areas, including a set of cognitive-behavioral interventions with speech, occupational, and physical therapies, as well as, in some cases, pharmacological treatments. From the cognitive perspective, the aim is to provide a systematic and regular approach, which encourages the application of the child's self-regulatory skills in a variety of social situations.[xl,xli]

Although there are currently no approved medications for the management of the core symptoms of ASD, psychopharmacological treatment is used to address other common symptoms in patients with autism.[xviii] This includes the use of stimulants, alpha-2 agonists, anticonvulsants, and antidepressants for the intervention of symptoms such as hyperactivity, inattention, impulsivity, irritability, aggression, self-injurious behavior, repetitive behaviors, and insomnia. In addition, antipsychotics such as risperidone and aripiprazole are licensed for the management of irritability associated with the disorder.[xlii]

Given the extensive role of glutamate in neurotransmission and its connection to the development of various pathologies, clinical trials have been conducted using several drugs that block NMDA receptors, a ionotropic subtype of glutamate receptors.[xliii] This has made it possible to establish links between these receptors and central nervous system disorders such as epilepsy, pain, ischemia, addictions, neurodegenerative diseases, and social deficits.[xliv-xlvi]

Recognition of the involvement of glutamate in various neurological conditions has prompted the search and investigation of

drugs that specifically modulate the glutamatergic pathway, with a focus on metabotropic glutamate (mGlu) receptors. Special attention has been given to memantine, which acts on NMDA receptors.[xlvii] Memantine is a non-competitive antagonist with a remarkable selectivity for NMDA receptors in the brain. This action allows it to restore physiological glutamatergic neuronal transmission and ameliorate the pathological effects associated with elevated synaptic glutamate concentrations.[xlviii]

Hardan *et al.*, in their double-blind study, compared memantine treatment of children with ASD; half of the participants received memantine as an adjuvant, while the other half received only a placebo. The study focused on evaluating the efficacy and safety of memantine in children with autism. In terms of safety, the study found that 64 % of individuals experienced mild adverse effects, such as dizziness, headache, fatigue, nausea, constipation, or diarrhea. In comparison, only 0.7 % experienced serious effects that resulted in treatment discontinuation.[vii]

An improvement in social responsiveness was observed in all study groups (memantine and placebo). However, after the end of treatment, participants who received a placebo or a reduced dose showed a worsening on the Social Responsiveness Scale (SRS), with increases of ten to 20 points over their scores during treatment. In addition, a higher percentage of placebo patients (73 %) had a significant increase in SRS score compared to those treated with reduced-dose (66.7 %) and full-dose memantine (64.3 %), suggesting that memantine may offer more sustained improvement in ASD symptoms.[vii]

In the clinical trial conducted by Soorya *et al.*, the use of memantine as an adjuvant compared to placebo in adolescents with autism was investigated to assess its impact on social skills. The results revealed a significant improvement in verbal recognition memory among participants treated with memantine. Furthermore, when analyzing the IQ of individuals who received memantine, a positive development in verbal IQ was observed after treatment.[viii]

This is consistent with the clinical trial conducted by Schiller, *et al.*, in 2023, in which the effect of memantine was examined in patients with epileptic encephalopathy, including ten patients who had previously been diagnosed with attention deficit hyperactivity disorder and eight patients previously diagnosed with autism spectrum disorder. During the study, significant improvements were identified in the electroencephalograms (EEGs) of the memantine-treated participants, including a reduction in the amplitude and frequency of epileptiform discharges, fewer nocturnal awakenings, and the absence of seizures on follow-up EEGs in two patients who initially had seizures. Less functional impairment was also observed in these participants, although no significant differences were found with respect to placebo.[ix]

In neuropsychological assessment, participants with ADHD and ASD treated with memantine showed lower scores on scales such as the Conners-3 ($p = 0.039$) compared to their baseline values. In contrast, the placebo group showed no significant changes ($p > 0.05$). In addition, those treated with memantine showed a reduction in global indices of impulsivity and emotional lability, suggesting an improvement in social and cognitive skills.[ix]

Due to this new research, therapies involving mGluR allosteric modulatory drugs can be extended to regulate neuronal excitability and synaptic conduction selectively. This allows for reduced behavioral and cognitive effects characteristic of many brain disorders such as ASD and improves the social responsiveness of patients.[x] Although a direct relationship between the reduction of ASD symptoms and the use of glutamate receptor allosteric drugs has not been demonstrated, some research has concluded that there is an improvement in certain social abilities, which is an important precedent for future studies.

Conclusion

Autism spectrum disorder is a complex condition that encompasses a variety of disorders that share characteristics such as difficulties in social communication, restricted behaviors, and the display of repetitive behaviors. Research has highlighted the role of glutamate in this disorder, demonstrating that alterations in its function are significant in the development of the disorder. These alterations affect communication between neurons and, consequently, contribute to the symptoms of autism, including difficulties in social interaction and repetitive behavior patterns. Due to experimental studies, both at the preclinical and clinical level, it is possible to verify that therapies with allosteric modulator drugs of metabotropic receptors manage to selectively regulate neuronal excitability and synaptic conduction, which allows less behavioral and cognitive effects typical of autism spectrum disorder and helps its social responsiveness, especially at a verbal level.

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References

i. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Arlington, VA.: American Psychiatric Association; 2013. 50-59 p.
ii. Oakley B, Loth E, Murphy D. Autism and mood disorders. Int Rev Psychiatry. 2021 33(3):280-299. DOI: 10.1080/09540261.2021.1872506
iii. Organización Mundial de la Salud. Autismo. OMS. 2023. Consulted date: April 6, 2025. Available at: https://www.who.int/es/news-room/fact-sheets/detail/autism-spectrum-disorders
iv. Maenner M, Shaw K, Baio J, Washington A, Patrick M, DiRienzo M, et al Prevalence of autism spectrum disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. MMWR Surveill Summ. 2020; 69 (4):1-12 Available at: https://www.cdc.gov/mmwr/volumes/69/ss/ss6904a1.htm
v. Satterstrom F, Kosmicki J, Wang J, Breen M, De Rubeis S, An J, *et al.* Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. Cell. 2020;180(3):568-584.e23. DOI: 10.1016/j.cell.2019.12.036
vi. Wang L, Wang B, Wu C, Wang J, Sun M. autism spectrum disorder: Neurodevelopmental Risk Factors, Biological Mechanism, and Precision Therapy. Int J Mol Sci. 2023;24(3):1819. DOI: 10.3390/ijms24031819
vii. Hardan A, Hendren R, Aman M, Robb A, Melmed R, Andersen K, *et al.* Efficacy and safety of memantine in children with autism spectrum disorder: Results from three phase 2 multicenter studies. Autism. 2019;23(8):2096-111. DOI: 10.1177/1362361318824103
viii. Soorya L, Fogg L, Ocampo E, Printen M, Youngkin S, Halpern D, *et al.* Neurocognitive Outcomes from Memantine: A Pilot, Double-Blind, Placebo-Controlled Trial in Children with autism spectrum disorder. J Child Adolesc Psychopharmacol. 2021;31(7):475-484. DOI: 10.1089/cap.2021.0010
ix. Schiller K, Berrahmoune S, Dassi C, Corriveau I, Ayash T, Osterman B, *et al.* Randomized placebo-controlled crossover trial of memantine in children with epileptic encephalopathy. Brain. 2023;146(3):873-879. DOI: 10.1093/brain/awac380
x. Luessen D, Conn P. Allosteric Modulators of Metabotropic Glutamate Receptors as Novel Therapeutics for Neuropsychiatric Disease. Pharmacol Rev. 2022;74(3):630-661. DOI: 10.1124/pharmrev.121.000540
xi. Escobar L, Sánchez C, Andrade J, Saltos L. El trastorno del espectro autista (tea) y los métodos de enseñanza para niños en el aula de clases. Digital Publisher CEIT. 2024;9(1-1):82-98. DOI: 10.33386/593dp.2024.1-1.2263
xii. Gómez- M. Conexión neuronal en el trastorno del espectro autista. Psiquiatr Biol. 2019;26(1):7-14. DOI: 10.1016/j.psiq.2019.02.001
xiii. Yáñez C, Maira P, Elgueta C, Brito M, Crockett M, Troncoso L, *et al.* Estimación de la prevalencia de trastorno del aspectro autista en población urbana chilena. Andes pediatr. 2021;92(4):519-525. DOI: 10.32641/andespediatr.v92i4.2503
xiv. Espín J , del Valle M, Espín Jaime F. Lo que es trastorno del espectro autista y lo que no lo es. An Pediatr Contin. 2013;11(6):333-341. DOI: 10.1016/S1696-2818(13)70155-0
xv. Waizbard E, Fein D, Lord C, Amaral D. Autism severity and its relationship to disability. Autism Res. 2023;16(4):685-696. DOI: 10.1002/aur.2898
xvi. Reyes E, Pizarro L. Rol de la terapia farmacológica en los trastornos del espectro autista. Revista Médica Clínica las Condes. 2022;33(4):387-99. DOI: 10.1016/j.rmclc.2022.07.002
xvii. Zhang D, Hua Z, Li Z. The role of glutamate and glutamine metabolism and related transporters in nerve cells. CNS Neurosci Ther. 2024;30(2):e14617. DOI: 10.1111/cns.14617
xviii. Genovese A, Butler M. The autism spectrum: Behavioral, Psychiatric and Genetic Associations. Genes (Basel). 2023;14(3):677. DOI: 10.3390/genes14030677
xix. Vásquez B, del Sol M. Rol de la Neuroglia en el trastorno del espectro autista. International Journal of Morphology. 2021;39(3):920-927. DOI: 10.4067/S0717-95022021000300920.
xx. Egbenya D, Aidoo E, Kyei G. Glutamate receptors in brain development.

Childs Nerv Syst. 2021;37(9):2753-8. DOI: 10.1007/s00381-021-05266-w

xxi. Marotta R, Risoleo M, Messina G, Parisi L, Carotenuto M, Vetri L, *et al.* The Neurochemistry of Autism. Brain Sci. 2020 ;10(3):163. DOI: 10.3390/brainsci10030163

xxii. Khalifa D, Shahin O, Salem D, Raafat O. Serum glutamate was elevated in children aged 3-10 years with autism spectrum disorders when they were compared with controls. Acta Paediatrica. 2019;108(2):295-9. DOI: 10.1111/apa.14477

xxiii. Takado Y, Sato N, Kanbe Y, Tomiyasu M, Xin L, Near J, *et al.* Association between Brain and Plasma Glutamine Levels in Healthy Young Subjects Investigated by MRS and LC/MS. Nutrients. 2019;11(7):1649. DOI: 10.3390/nu11071649

xxiv. Sears SM, Hewett SJ. Influence of glutamate and GABA transport on brain excitatory/inhibitory balance. Exp Biol Med (Maywood). 2021;246(9):1069-83. DOI: 10.1177/1535370221989263

xxv. Port R, Oberman L, Roberts T. Revisiting the excitation/inhibition imbalance hypothesis of ASD through a clinical lens. Br J Radiol. 2019;92(1101):20180944. DOI: 10.1259/bjr.20180944

xxvi. Edmondson D, Xia P, Keehn R, Dydak U, Keehn B. A magnetic resonance spectroscopy study of superior visual search abilities in children with autism spectrum disorder. Autism Res. 2020;13(4):550-562. DOI: 10.1002/aur.2258

xxvii. Ajram L, Horder J, Mendez M, Galanopoulos A, Brennan L, Wichers R, *et al.* Shifting brain inhibitory balance and connectivity of the prefrontal cortex of adults with autism spectrum disorder. Transl Psychiatry. 2017;7(5):e1137. DOI: 10.1038/tp.2017.104

xxviii. Bhandari R, Paliwal JK, Kuhad A. Neuropsychopathology of Autism Spectrum Disorder: Complex Interplay of Genetic, Epigenetic, and Environmental Factors. Adv Neurobiol. 2020;24:97-141. DOI: 10.1007/978-3-030-30402-7_4

xxix. Morland C, Nordengen K. N-Acetyl-Aspartyl-Glutamate in Brain Health and Disease. International Journal of Molecular Sciences. 2022;23(3):1268. DOI: 10.3390/ijms23031268

xxx. Nisar S, Bhat A, Masoodi T, Hashem S, Akhtar S, Ali TA, *et al.* Genetics of glutamate and its receptors in autism spectrum disorder. Mol Psychiatry. 2022;27(5):2380-2392. DOI: 10.1038/s41380-022-01506-w

xxxi. Nicosia N, Giovenzana M, Misztak P, Mingardi J, Musazzi L. Glutamate-Mediated Excitotoxicity in the Pathogenesis and Treatment of Neurodevelopmental and Adult Mental Disorders. Int J Mol Sci. 2024;25(12):6521. DOI: 10.3390/ijms25126521

xxxii. Cai J, Ding L, Zhang JS, Xue J, Wang LZ. Elevated plasma levels of glutamate in children with autism spectrum disorders. Neuroreport. 2016;27(4): 272-276. DOI: 10.1097/WNR.0000000000000532

xxxiii. Baribeau D, Anagnostou E. Novel treatments for autism spectrum disorder based on genomics and systems biology. Pharmacology & Therapeutics. 2022;230:107939. DOI: 10.1016/j.pharmthera.2021.107939

xxxiv. Toledano A, Enriquez V, Naya S, Briz V, Alfaro R, Parra M, *et al.* Enhanced mGluR5 intracellular activity causes psychiatric alterations in Niemann Pick type C disease. Cell Death Dis. 2024;15(10):771. DOI: 10.1038/s41419-024-07158-8

xxxv. Jójárt B, Orgován Z, Márki Á, Pándy-Szekeres G, Ferenczy G, Keserű G. Allosteric activation of metabotropic glutamate receptor 5. J Biomol Struct Dyn. 2020;38(9):2624-2632. DOI: 10.1080/07391102.2019.1638302

xxxvi. Rafiee F, Rezvani R, Motaghi M, Yousem D, Yousem I. Brain MRI in autism spectrum disorder: Narrative Review and Recent Advances. Journal of Magnetic Resonance Imaging. 2022;55(6):1613-1624. DOI: 10.1002/jmri.27949

xxxvii. Su LD, Wang N, Han J, Shen Y. Group 1 Metabotropic Glutamate Receptors in Neurological and Psychiatric Diseases: Mechanisms and Prospective. Neuroscientis. 2022;28(5):453-468. DOI: 10.1177/10738584211021018

xxxviii. Carey C, Singh N, Dunn J, Sementa T, Mendez M, Velthuis H, *et al.* From bench to bedside: The mGluR5 system in people with and without autism spectrum disorder and animal model systems. Transl Psychiatry. 2022;12:(1)395. DOI: 10.1038/s41398-022-02143-1

xxxix. Dogra S, Conn P. Metabotropic Glutamate Receptors As Emerging Targets for the Treatment of Schizophrenia. Mol Pharmacol. 2022;101(5):275-285. DOI: 10.1124/mol pharm.121.000460

xl. Centro para el control y la prevención de las enfermedades CDC. Tratamientos e intervenciones para los trastornos del espectro autista. 2024. Consulted date: April 6, 2025. Available at: https://www.cdc.gov/autism/es/treatment/tratamientos-e-intervenciones-para-los-trastornos-del-espectro-autista.html

xli. Barris N, Rubiales J, Labandal L. Estrategias conductuales en niños y niñas con trastorno del espectro autista: una revisión sistemática. Actualidades en

Psicología. 2023;37. DOI: 10.15517/ap.v37i134.51016
xlii. Henneberry E, Lamy M, Dominick K, Erickson C. Decades of Progress in the Psychopharmacology of autism spectrum disorder. J Autism Dev Disord. 2021;51(12):4370-4394. DOI: 10.1007/s10803-021-05237-9
xliii. Groc L, Choquet D. Linking glutamate receptor movements and synapse function. Science. 2020;368(6496):eaay4631.DOI: 10.1126/science.aay4631
xliv. Huang L, Xiao W, Wang Y, Li J, Gong J, Tu E, *et al.* Metabotropic glutamate receptors (mGluRs) in epileptogenesis: an update on abnormal mGluRs signaling and its therapeutic implications. Neural Regen Res. 2023;19(2):360-368. DOI: 10.4103/1673-5374.379018
xlv. Kim J, Kang S, Choi T, Chang K, Koo J. Metabotropic Glutamate Receptor 5 in Amygdala Target Neurons Regulates Susceptibility to Chronic Social Stress. Biol Psychiatry. 2022;92(2):104-115. DOI: 10.1016/j.biopsych.2022.01.006
xlvi. Dogra S, Conn P. Targeting metabotropic glutamate receptors for the treatment of depression and other stress-related disorders. Neuropharmacology. 2021;196:108687. DOI: 10.1016/j.neuropharm.2021.108687
xlvii. Zohny S, Habib M, Mohamad M, Elayat W, Elhossiny R, El-Salam M, *et al.* Memantine/Aripiprazole Combination Alleviates Cognitive Dysfunction in Valproic Acid Rat Model of Autism: Hippocampal CREB/BDNF Signaling and Glutamate Homeostasis. Neurotherapeutics. 2023;20(2):464-483. DOI: 10.1007/s13311-023-01360-w
xlviii. Kuns B, Rosani A, Patel P, Varghese D. Memantine. StatPearlsPublishing. 2024. Available at: http://www.ncbi.nlm.nih.gov/books/NBK500025/