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Review

Glutamate Receptor Activity in Neuropsychiatric Disorders

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ABSTRACT

Glutamate, a non-essential amino acid, is important for the central mammalian nervous system. It is released into the synaptic cleft from the presynaptic membrane of neurons by vesicles carrying the glutamate protein and is retained by the glutamate receptors of the postsynaptic neuron and takes part in synaptic transmission. Any mutation or change in expression that occurs in the ionotropic and metabotropic receptors, subtypes of glutamate receptors, can cause the development of neuropsychiatric disorders. The aim of the review was to give information about glutamate receptors and their function in psychiatric diseases.

Keywords: Glutamate, glutamate receptors, neuropsychiatric disorders, receptor mutations

Chemical messengers in the human nervous system are called neurotransmitters.[1] which are responsible for the neurological regulation of the brain; are found in biological fluids in the human body, such as plasma, serum, cerebrospinal fluid (CSF), saliva, and urine. There are more than 60 chemicals present in the nervous system that act as neurotransmitters. Neurotransmitters are synthesized from a neuron and released into the synaptic cavity due to the storage of the nerve cell terminal and are released to be connected to the receptors from the presynaptic neuron to the postsynaptic neuron. The first discovered acetylcholine[2] is the neurotransmitter acting as a platelet inhibitor.[3] The latter discovery of L-glutamate is an amino acid that acts as an intermediate for the stimulating signals in the mammalian central nervous system and whose primary function is closely related to brain functions such as cognition, memory, and learning. It is also responsible for cell migration, differentiation, and cell death. Glutamate, which is capable of signaling in peripheral organs and tissues and endocrine cells, is abundant in brain cells in the amount of about 5-15 mmol per kg, which varies depending on the brain region. It is in small quantities in the extracellular region, which is extracellular or intercellular.[4,5]

GLUTAMATE METABOLISM IN THE BRAIN

Glutamate is involved in reactions as a substrate or product and is synthesized by many metabolic pathways. N-acetyl-L-glutamate is involved in the synthesis of products such as δ[1]-pyrroline-5-carboxylate, β-citrine glutamate, L-γ-Glutamyl-L-cysteine.[6]

Vesicles carrying the glutamate protein release the glutamate from the neuron presynaptic membrane into the synapse cavity and from there are held by the glutamate receptors of the postsynaptic neuron. Excess glutamate is converted into the compound needed through many different means. It is taken back to the presynaptic terminal and converted to alpha-ketoglutarate with the help of the glutamate dehydrogenase enzyme, then it plays a role in the Krebs cycle again. Glutamine can be synthesized from glutamate with the enzyme glutamine synthesis, or it can be released into the extracellular range with cystine/glutamate antiport systems and take part in the cycle.[7]

The conversion of glutamate (Glu) to glutamine (Gln) can also be synthesized *de novo* by glucose transamination from the α-oxoglutarate compound.[8]

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Excitatory amino acid transporters (EAAT) located in the central nervous system keep the glutamate concentrations outside the cell at a certain level and help clean the environment by reclaiming excess glutamate with EAATs.[9]

GLUTAMATE TRANSPORTERS

Excitatory amino acid transporters in the transporter family associated with glutamate, vesicular glutamate transporters (VGLUTs), and glutamate-cysteine exchangers are available. EAATs, called Na+ dependent glutamate transporters, keep the extracellular concentration at excitotoxic levels by blocking the action of unnecessary glutamate in neuron and glial cell plasma membranes.[10] The transport of Na+ dependent L-glutamate has long been a matter of discussion. It has been tried to be clarified by cloning on the translocation of the protein family, which consists of carrier molecules, to the plasma membrane of the substrates it carries. Substrate binding sites on carrier molecules are preferred molecules such as glutamate or aspartate that contain one positive charge and two negative charges. Moreover, glutamate transporters are associated with neuronal loss due to damage to brain tissues such as cerebral ischemia, and Alzheimer's disease (AD).[11] Furthermore, EAATs found in the surrounding glial cells and plasma membranes address neuronal damage induced by glutamate receptor activity in addition to providing extracellular concentration retention.

Structurally, there are five glutamate transporter subtypes, EAAT1 (GLAST), EAAT2 (GLT-1), EAAT3 (EAAC1), EAAT4, and EAAT5. As a result of the transport of glutamate by EAATs, thermodynamic balance is achieved with the input of proton and the output of a K+ ion with two or more Na+ ions. Thus, as a result of glutamate transport, at least one proton enters the cell against glutamate.[12]

EAAT1 (GLAST) and EAAT2 (GLT-1) were the first to be cloned from rat brains with 65% amino acid identity.[13] EAAT2 is responsible for a large proportion (≥90%) of total transported glutamate to synaptosomes. It is expressed in astrocytes and helps to prevent excitotoxic neuronal damage that causes neurodegenerative disorders by keeping glutamate concentrations at certain levels. EAAT1; Apart from organs such as the retina, the cerebellum acts as the main transporter of glutamate in the brain.[14,15] EAAT2, on the other hand, is known to play a role in the activation of retinal cells thanks to the anion flow that occurs with EAAT5 expressed in the retina, and it is known to affect the membrane potential and synaptic release of retinal bipolar cells.[16] EAAT5 acts in neurons as an inhibitory glutamate-gated chloride channel.[17] EAAT4 acts as a glutamate carrier in the cerebellum region and is responsible for the control of voluntary muscle movements. Studies have been associated with the pathogenesis of motor system disorders such as tremor/ataxia syndrome associated with spinocerebellar ataxia (SCA), episodic ataxia type-6, spinal muscular atrophy, and fragile X syndrome (FXS) as a result of loss of expression of EAAT4 and/or EAAT1.[18] EAAT3, the first glutamate carrier, has fewer roles related to this task, unlike EAAT1 and EAAT2, which have a direct role in releasing glutamate through the extracellular cavity.[19] EAAT3 is usually found on the surface of dendrites.[20] Expression is seen in mature or immature neurons, which are also abundant in presynaptic/postsynaptic membranes. When necessary, it is transported to the plasma membrane with Rab11, and SNAP-23 thus activating the protein that acts as a transporter in the membrane.[21]

During neurotransmission, synaptic vesicles in the neuron cell are involved in taking the compound with endocytosis and then releasing it into the synaptic cavity through exocytosis. The transport of glutamate by synaptic vesicles with endocytosis is provided by VGLUT.[22] VGLUT1, VGLUT2, and VGLUT3 are three kinds of VGLUT that are comparable in sequence, pharmacological, and kinetic aspects. It helps the synaptic transmission of glutamate by stimulating vesicles and/or vacuoles as a result of the difference between proton and electrochemical gradient produced by H+-ATPase. Although VGLUTs have similar characteristics, there are differences due to increased and decreased expression. For VGLUT1, expression is more observed in the cerebral and cerebellar cortexes in the hippocampus [23], which is associated with memory, learning, and emotions, while VGLUT2 shows expression in the diencephalon, brainstem, and spinal cord. Despite isoforms of VGLUT1 or VGLUT2 being expressed, studies have shown that both are expressed in cerebellar mossy fiber terminals and cerebellar unipolar brush cells. VGLUT3, the other third isoform, is expressed less than other VGLUTs.[24] While VGLUT3 is not expressed in glutamatergic neurons, it is usually expressed in neurons that use neurotransmitters such as serotonin[25], acetylcholine, or GABA. They act as diagnostic markers in glutamatergic transmission with increased or decreased expression levels of VGLUT. The observed expression levels of VGLUT1 are associated with diseases such as anxiety, Parkinson's

disease[26,27], mood disorder, AD[28], and epilepsy whereas VGLUT2 is associated with schizophrenia and neuropathic pain. VGLUT2 was associated with decreased expression level and decreased motoneuron degeneration in mice with amyotrophic lateral sclerosis. In addition, tau mouse models with AD had an increase of up to 40% in VGLUT1 expression level and glutamate amount.[29]

GLUTAMATE RECEPTORS

Glutamate receptors in presynaptic and postsynaptic neurons, which play a role in the central nervous system, are divided into two groups: ionotropic (iGluR) and metabotropic receptor (mGluR) according to pharmacological characteristics. Ionotropic receptors are multimeric ion channels and are responsible for the rapid transmission of mammals in the central nervous system.[30] In addition, they are integral membrane proteins consisting of four large subunits located in the ion channel. The ionotropic receptor consists of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, N-methyl-D-aspartate (NMDA), and their groups. Glutamate receptors structurally consist of an extracellular amino-terminal domain, extracellular ligand-binding domain, transmembrane domain (TMD), and an intracellular carboxyl-terminal domain.[31] Metabotropic receptors are called G-protein coupled receptors and are targeted as therapeutic agents. There are eight mGluR subtypes and they are grouped under three groups; transduction mechanism, homology, and pharmacology. Group I, mGlu1 and mGlu5; Group II, mGlu2 and mGlu3; Group III includes mGlu4, mGlu6, mGlu7 and mGlu8.[32]

RECEPTOR MUTATIONS

Mutations in genes encoded in iGluRs including subgroups NMDAR, kainate receptor (KAR), and AMPA receptor (AMPAR) lead to abnormal glutamatergic synaptic transmission, resulting in some disorders such as intellectual disability (ID), developmental delay (DD), autism spectrum disorder (ASD). The mutations in the genes encoding GluA1, GluA3, and GluA4, which are sub-units of the AMPAR, may rarely contribute to the development of neurodevelopmental disorders (NDDs). Some changes in the expression of the GluA2 subunit encoded by the GRIA2 gene or alternative splicing have important implications for the incidence of FXS and diseases such as Rett syndrome (RTT).[33] The subunits of NMDA receptors, encoded by the GRIN gene family, GluN1, GRIN1's product; GluN2 GRIN2A are products of GRIN2B, GRIN2C and GRIN2D, and GluN3, GRIN3 and GRIN3B. More than 200 variants of GluN2B are seen in patients with schizophrenia, AD[34], cerebral visual impairment (CVI), DD, and attention deficit hyperactivity disorder (ADHD). In addition, some patients show abnormalities in muscle tone, microcephaly, RTT-like symptoms, and speech disorders in various phenotypes. Variations of the GRIN2B gene are thought to be associated with autism.[35] Studies have shown that GRIN2A is associated with NDD such as epileptic encephalopathy (EE) and epilepsy aphasia spectrum.[36] Pierson et al.[37] reported that the treatment of NMDAR expression with the GRIN2A mutation reduced expression and memantine would be used as antiepileptic, reducing epilepsy seizures. Studies for GRIN2B have concluded that knockout mice are fatal in newborns. The mutation in GRIN2B is observed with the appearance of synaptic plasticity in neuronal transmission. It causes variants in GRIN2B to have NDDs such as ID, ASD, EE, schizophrenia, CVI, and AD.[38]

RECEPTOR-DISEASE RELATIONSHIP

Ionotropic Receptors

N-Methyl-D-Aspartic Acid Receptors (NMDAR)

Schizophrenia is a psychiatric disorder associated with the deterioration of the development of the brain influenced by genetic and/or environmental factors and associated with symptoms such as decreased normal functions of the patient, avulsion[39], delusions, hallucinations, and disorganized speech, catatonia, anhedonia.[40] As a result of the studies, it has been revealed that there is a relationship between NMDA and schizophrenia.

NMDA receptors have a heterotetrameric structure and consist of one or two GluN1s copied from the GRIN1 gene, two or three GluN2 encoded from the GRIN2 gene, and/or GluN3 subunits encoded from the GRIN3 gene. NMDA receptors are ligand-gated cationic channels, and upon activation, they bind L-glycine or D-serine to GluN1 or GluN3, respectively, and glutamate to GluN2 subunits at the same time. Among the tasks of NMDARs, they provide glutamatergic neurotransmission in mature cortical neurons and are of great importance in learning and memory skills.[41]

NMDARs are involved in various physiologies of the human body, balancing cellular homeostasis. Therefore, any contrary condition in the receptors can lead to the formation of diseases such as AD, ALS, Huntington's disease (HD), PD, schizophrenia, and major depressive disorder (MDD). [42-44]

Studies have shown that schizophrenia is associated with NMDA receptor hypofunction, and anesthetic agents such as phencyclidine or 1-(1-phenylcyclohexyl) piperidine (PCP) and ketamine, which are antagonists in NMDA, induce positive, negative, and cognitive characteristics in schizophrenia patients, and ketamine exacerbates symptoms in patients.[45] It has been argued in the NMDA receptor hypofunction hypothesis (NRHypo) that schizophrenia symptoms can be observed by drugs that are applied to human or animal models by NMDA antagonist drugs, thereby facilitating the schizophrenia mechanism in human or animal models.[46] Researchers carrying out studies for NRHypo have created therapeutic models of schizophrenia in animals that do not have any problems. In this way, studies on schizophrenia symptoms are carried out by realizing schizophrenia in animals. NMDA receptor antagonists such as PCP and ketamine in schizophrenia have been found to trigger psychosis in volunteer human subjects, where it exacerbates symptoms.[47] Studies on magnetic resonance spectroscopy (MRS) and micro-dialysis have demonstrated that ketamine and other NMDAR antagonists have an effect on transmission by stimulating glutamate and acetylcholine release. SKF-10047 is a sigma-1 agonist as well as an NMDA antagonist[48], which is described as causing symptoms of schizophrenia. As NMDA receptors are blocked, excessive glutamate and acetylcholine release is expected to increase in the cerebral cortex. Followed by the release of transmitters, which cause over-inducing of postsynaptic neurons, the symptoms of the disease are consequent. Genetic and environmental factors may also influence NRHypo, potentially triggering psychosis.[49]

AMPA receptors

AMPA receptors (AMPARs) are glutamate-gated ion channels that mediate synaptic transmission. It is made up of four subunits (GluA1-4) in a tetramer structure to create the ion channel.[50]

The roles of the four subunits of AMPARs are to regulate AMPAR traffic[51], concentrated in the postsynaptic density region of PSD to provide fast synaptic density. This may change the PSD region layout depending on the AMPA sub-units. In hippocampal synapses, GluA1 is more concentrated by the PSD edge, while the GluA3 subunit is more central.[52] AMPA receptor antagonists have an important function in central signaling and are used for the treatment of epilepsy and ischemia. In addition, AMPA receptors have been found to play a critical role in the formation of epilepsy.[53]

Epilepsy is a chronic brain disease characterized by repeated attacks of seizures in the patient. Men are more prevalent and incidental than women.[54] Epilepsy occurs in all ages and genders, creating social, behavioral, health, and economic issues for patients and their families.[55] AMPA receptor antagonists have a broad anticonvulsant (antiepileptic) effect and have more effect on preventing seizures than NMDA antagonists. In the Kindling epilepsy models, AMPA receptor antagonists were thought to have an effect on epilepsy and studies concluded that despite resistance to diazepam, it could be effective for the treatment of status epilepticus.[56] Ionotropic glutamate receptor agonists have been proven in experiments performed as convulsants, leading to the development of ictogenesis in NMDA and AMPA receptors. Further, Kainate, (RS)-2-amino-3-(3-hydroxy-5-tert-butyl isoxazol-4-yl) propanoic acid (ATPA) and NMDA receptors and induced rodents display clonus and tonus.[57]

Autoantibodies are attached to the surfaces of proteins such as neurotransmitter receptors and appear to be associated with autoimmune encephalitis. Studies have identified the presence of Rasmussen's encephalitis in autoantibody serum, which recognizes GluA3, a sub-unit of AMPAR, and in some of the patients affected by different types of epilepsy (20% to 30%). It was concluded that the autoantibody anti-GluA3 antibodies cause learning, attention deficit, and the formation of certain psychiatric diseases. Frontotemporal dementia (FTD); a behavioral and speech disorder is a heterogeneous disease characterized by changes in personality. With the existence of autoantibodies against the GluA3 sub-unit which is owned by the AMPAR in approximately 20-25% of the patients with this disease, it was concluded that autoantibodies in some neurodegenerative disorders led to the disease progression.[58] Studies have resulted in the identification of anti-AMPA GluA3 antibodies in serum and CSF of patients with FTD, negatively affecting glutamate neurotransmission.[59] In the study Borroni et al.[60] conducted, anti-GluA3 antibody levels were higher in the serum of FTD patients than in healthy controls, causing Tau proteins to accumulate in vitro glia and neuron cells. A study conducted by Palese et al.[61] with FTD-tau patients investigated the effects of GluA3 autoantibodies on glutamatergic neurotransmission, and found that it reduced glutamate levels and caused changes in AMPA receptor levels. Thus, this is important for FTD patients, and it is concluded that there are abnormalities in glutamatergic neurotransmission.

Kainate receptors

Glutamate receptors such as KAR, AMPA, and NMDA are from the ionotropic receptor family and have also been reported to have metabotropic properties through some studies. Kainate receptors consist of five subunits, GluK1-GluK5. GluK1-3 is homomeric, while GluK4 and GluK5 and GluK1-3 are heteromeric. Hippocampal KARs containing GluK1 sub-units are expressed in internals. Kainate receptors with a GluK2 sub-unit are usually expressed in stimulating neurons, controlling the release of glutamate between presynaptic and postsynaptic neurons.

Temporal lobe epilepsy (TLE) is the most common type of epilepsy in humans. Usually, recurrent TLE seizures can be caused by the hippocampus and can also spread to the amygdala or the entorhinal cortex. Anticonvulsant drugs used for TLE disease stimulate transmission or provide GABAergic inhibition by acting on The Ca+2 channels with voltage-gated Na+ channels.[62] In the hippocampus, it is obliged to control GABA release.[63] In addition, in order to learn the effect of KAR on the epilepsy mechanism, Mulle et al.[64] created mutant mice with no GluK2 subunits, triggering epileptic seizures, and GluK2 sub united KAR were found to be important for synaptic transmission and status epilepticus. Fritsch et al.[65], in a study on how GluK1-containing KARs play a role in epileptogenesis; ATPA, the agony of KAR containing the GluK1 subunit, used mice with suppressed genes of the GluK1 and GluK2 KAR subunits. Locomotor, a prominent feature of ATPA's GluK1 activation, causes arrest, thus triggering myoclonic behavioral seizures.

Metabotropic glutamate receptors (mGluRs)

Metabotropic receptors are C-G-grade protein-coupled receptors located in the central nervous system that provides control in synaptic transmission and plasticity. Metabotropic receptors consist of seven TMDs. In addition, the protein is divided into three different groups according to binding and pharmacological properties. Group I members called mGlu1 and mGlu5 bind to Gq-like proteins, increasing intrasellar Ca+2 levels and enabling the activation of protein kinase C; Group II members with mGlu2 and mGlu3 and group III members containing mGlu4, mGlu6, mGlu7, and mGlu8 are bound by Gi/Go proteins and inhibit adenylate cyclase, which leads to a decrease in cyclic adenosine monophosphate (cAMP) and inactivation of protein kinase A. In terms of localization, mGlu receptors may vary depending on their region. While mGlu6 is usually expressed in the retina, other receptors are mostly expressed in the brain. In addition, mGlu3 and mGlu5 are expressed in glial cells. Group I mGlu receptors in postsynaptic regions; Group II and Group III receptors are expressed in presynaptic axon terminals.[66]

NDD formation, such as Down syndrome, Rett syndrome, FXS, and Angelman syndrome, can cause spot mutations, deletions, and duplications.[67] In the studies, new variants were observed in the KIF5B, GRM7, FOXP4, MLLT1, and KDM2B genes that cause neurodegenerative disorders as a result of the investigation of Arabic families with intellectual disabilities and brain malformations consisting of 13 men and 18 women and their close relatives.[68] In addition, mGluRs are known to play a role in the formation of epilepsy. In epilepsy models of Group I mGlu receptors (mGluR), agonists are proconvulsive, while antagonists have anticonvulsant effects. The contrary is not evident in Group II and Group III members. MGluR7, encoded by the GRM7 gene, is expressed in the central nervous system. In synapses, glutamate and inhibitory neurotransmitter GABA are involved in synaptic transmission, inhibiting excess oscillation. When stimulated by spontaneous stimuli in studies with mGluR7-knockout mice, epilepsy can be triggered as a result of changes in GRM7 expression.[69,70]

In conclusion, glutamate causes neuronal cell death by overstimulation of NMDA receptors, thus leading to the observation of psychiatric diseases. Among the main causes of neurodegenerative disorders are disruptions in the glutamate neurotransmission mechanism in brain regions resulting from structural changes in receptors and their binding sites, and changes in the gene expression mechanism of receptors. In addition, it is observed in many studies that glutamate neurotransmitter structures cause ototoxicity because of the release of synaptic cavities and inadequate retransmission of these neurotransmitters to cells. Excitotoxicity triggers the onset of neurodegenerative disorders. It is seen that it interacts with glutamatergic pathways and has an important place in the etiology and treatment of neuropsychiatric diseases. Drugs targeting glutamate excitotoxicity (memantine, etc.) are considered to reduce glutamate secretion by using drugs on model animals and their effect on glutamate carriers. However, the glutamate receptor's mechanism of action has not been fully understood in medications and diseases, and its effect on environmental stress has been a major factor in such psychiatric disorders. Thus, it is necessary to continue the development

of effective and target drugs that will benefit neurodegenerative disorders until studies that will help understand brain diseases at the cellular level are completed.

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