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Review

A Physiological Perspective on Glutamate and its Receptors

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ABSTRACT

Glutamate operates as the principal stimulator neurotransmitter in the mammalian central nervous system and is essential for cognitive functions, memory, and learning processes. It serves as a metabolic precursor of γ-aminobutyric acid (GABA) and is a constituent of the antioxidant glutathione. The glutamate-glutamine cycle regulates glutamate levels by facilitating its recycling between astrocytes and neurons. Glutamate is conveyed into synaptic vesicles by vesicular glutamate transporters (VGLUT) and is discharged into the synaptic cleft during neuronal depolarization. Extracellular glutamate is taken away from the synapse by excitatory amino acid transporters (EAAT), particularly those found in astrocytes, which help maintain glutamate homeostasis and prevent excitotoxicity. Glutamate receptors are fundamentally categorized into two primary classes: ionotropic (NMDA, AMPA, Kainate, Delta) and metabotropic. Ionotropic glutamate receptors (iGluRs) mediate fast excitatory responses, with N-methyl-D-aspartate (NMDA) receptors playing a key role in processes like synaptic plasticity and long-term potentiation (LTP) through calcium (Ca^{2+}) influx. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are crucial for rapid synaptic transmission and for the activation of NMDA receptors. Metabotropic receptors regulate intracellular signaling pathways via G-protein-coupled mechanisms. Dysfunction in the glutamate system is linked to various neurological disorders such as epilepsy, autism spectrum disorders, schizophrenia, and depression. Excess glutamate accumulation can lead to excitotoxicity and cell death. Furthermore, sex differences in glutamate levels may explain the varying impacts of neurological disorders across genders. Glutamate receptor agonists and antagonists present potential drug targets for treating glutamatergic system-related pathologies. Ketamine, memantine, riluzole, and D-cycloserine (DCS) are among the medicines employed in this domain. This review thoroughly analyzes the existing literature regarding the function of glutamate in the central nervous system. This review focuses on contemporary research on the association between glutamate receptors and neurological diseases. This study employs the literature review technique to offer a comprehensive perspective on the physiological and pathological roles of glutamate.

Keywords: Glutamate, glutamatergic system, ionotropic glutamate receptor, metabotropic glutamate receptor, synaptic plasticity

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INTRODUCTION

Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system (CNS), regulating 70-90% of synaptic transmission within the CNS.[1] It is made from α-ketoglutarate, which is a step in the Krebs cycle. The enzymes aspartate aminotransferase or glutamate dehydrogenase speed up the reaction.[2,3] It is considered the main neurotransmitter for neocortical and hippocampal

pyramidal neurons. With this feature, it is involved in mental functions such as cognition and memory. The brain contains higher concentrations of glutamate than other amino acids [4]. Glutamate is not only found in the central nervous system but also serves as a neurotransmitter present in various peripheral tissues such as the gastrointestinal system [5,6]. Glutamate serves as a metabolic precursor for γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain. It is also a component of other amino acid-derived chemicals, including glutathione, which functions as an antioxidant. Numerous metabolic investigations have demonstrated that nearly all glucose entering the brain is ultimately transformed into glutamate [7–9].

Not only does glutamate help send signals of excitement between presynaptic and postsynaptic sites, but it is also recycled and controlled by glial cells through excitatory amino acid transporters (EAATs) [10]. To make this cycle work, glutamine synthetase is first found in astrocytes, which are the main glial cells in the brain and spinal cord. It helps make glutamine from glutamate [11]. The glutamine is then sent to neurons by astrocytes. Enzymes called glutaminase or glutamate synthase in these neurons change glutamine back into glutamate. This creates a glutamate-glutamine cycle between astrocytes and neurons [12,13]. In summary, glutamate is partially recycled or degraded through the glutamate-glutamine cycle [14]. Glutamine also acts as a precursor for the biosynthesis of GABA, an inhibitory neurotransmitter [15]. Finally, astrocytes use glutamine to control the net production of glutamate and GABA, which are the two principal neurotransmitters for the nervous system [16].

Glutamate is broken down by the above-mentioned processes and then put into synaptic vesicles by vesicular glutamate transporters right after it is made. It is then released from these vesicles into the synaptic gap when neurons depolarize [1]. It passively diffuses into the synaptic cleft and attaches to presynaptic, postsynaptic, and perisynaptic glutamate receptors. Subsequently, extracellular glutamate is eliminated from the synapse through EAATs. Some of the extracted glutamate is reintroduced into synaptic vesicles by vesicular glutamate transporters (VGLUTs) [17].

VGLUTs primarily facilitate the absorption of extracellular glutamate into presynaptic vesicles for its storage. There exist three varieties of VGLUTs: VGLUT1, VGLUT2, and VGLUT3 [18]. VGLUT1 and VGLUT2 are located in glutamatergic neurons, but VGLUT3 predominantly resides in GABAergic, monoaminergic and cholinergic neurons [19]. It has also been said that VGLUT1 and VGLUT2 are present in glial cells and may help depolarized astrocytes release glutamate. It has been said that lower levels of VGLUT may slow down the flow of glutamate to synaptic vesicles and damage neurons. VGLUTs work by sending glutamate molecules to the synaptic cleft in a way that depends on Ca^{2+} cation and soluble N-ethylmaleimide-sensitive factor binding protein receptor (SNARE) [10].

Certain astrocyte transporters take synaptic glutamate out of the synaptic cleft when things are working normally [10]. In this case, EAATs are found at glutamatergic synapses and perisynaptic glial cells, and they play a big role in keeping glutamate levels stable [20,21]. The principal high-affinity glutamate transporters are identified as GLAST (EAAT-1), Glt-1 (EAAT-2), and EAAC-1 (EAAT-3). The astrocyte EAAT-2 and the glial glutamate transporter (GLT-1) in rats uptake extracellular glutamate and convert it into glutamine for cellular recycling [10]. EAAT-1 and EAAT-2 are predominantly expressed in astrocytes, whereas EAAT-3 is primarily expressed in neurons [16]. Given that EAAT-1 and EAAT-2 transport glutamate with more efficiency than EAAT-3, it is evident that astrocytes are responsible for the removal of glutamate from the synaptic cleft [22]. Excessive extrasynaptic glutamate receptor stimulation triggers apoptosis. EAATs, which are involved in the reabsorption of surplus glutamate in the extracellular space, are essential for preventing excitotoxicity [23]. When it comes to the central nervous system, the concentration of glutamate is highest within the cells themselves. The intracellular glutamate concentration is much higher than that of extracellular fluid, cerebrospinal fluid, or plasma. Since disturbances in the glutamatergic system can lead to deleterious effects, the concentration of glutamate in the brain is tightly maintained and regulated by many mechanisms, such as maintaining glutamate/glutamine balance by endothelial cells of the blood-brain barrier, neurons, and astrocytes [24]. In a healthy adult brain, a highly sensitive system maintains equilibrium between the excitatory and inhibitory actions of glutamate and GABA molecules [25]. This balance can be upset, and high levels of glutamate can make glutamate receptors stay active for longer. This can cause more calcium to enter neurons. This phenomenon is called excitotoxicity [26]. Increasing evidence supports the fact that excitotoxicity, glutamatergic dysfunction, and neuroinflammation may be closely related [27].

When glutamate is released, it sends a signal that can cause proinflammatory cytokines like tumor necrosis factor alpha (TNF-a) and interleukin-1 beta (IL-1b) to be released [28]. Glutamate enhances the release of cytokines; cytokines can also potentiate glutamate release. During neuroinflammatory processes, the number of astrocytes that express high-affinity glutamate transporters goes down. These transporters get rid of extra glutamate from the synaptic cleft. TNF-a increases synaptic currents that are excitatory by removing AMPA receptors from synapses and decreasing synaptic currents that are inhibitory by removing GABA receptors from synapses. This suggests an excitatory shift of the inhibition/excitation balance [24,29].

GLUTAMATE RECEPTORS

Following the discharge of glutamate molecules into the synaptic gap, activation of glutamate receptors occurs [30]. Glutamate acts on these receptors through a post-synaptic effect [31]. Glutamate receptors are divided into two different groups: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) (Table 1) [32]. iGluRs are a type of glutamate receptor that allows ions to enter and causes rapid stimulation. They have a binding site for an agonist. Some special brain cells called mGluRs work with long-term potentiation (LTP) and synaptic activity [10,33]. Both of these receptor types have a broad spectrum of effects [34].

Ionotropic Glutamate Receptors (iGluRs)

iGluRs are ligand-activated ion channels that facilitate rapid excitatory neurotransmission [35]. iGluRs are split into four groups based on which agonists they prefer [30]. These receptors are called NMDA receptors, AMPA receptors, Kainate receptors and Delta/Orphan receptors [36].

NMDA Receptors

NMDA receptors exhibit the strongest affinity for glutamate [37]. These receptors let three main cations (Na^+, K^+, and Ca^{2+}) pass through them for neurotransmission. They also have a part inside the cell that depends on mechanisms inside the cell, second messenger systems, and synaptic elements. On top of that, the same receptors have an extracellular N-terminal region that can bind ligands. The functional parts of the NMDA receptor are located between these two areas that make up the skeleton of the receptor. These functional parts are involved in the efflux mechanism [38]. When NMDA receptors are activated, the postsynaptic region has more Ca^{2+}, which causes synapses to change shape. LTP or long-term depression (LTD) can happen depending on how fast and how much Ca^{2+} enters through these receptors [39].

Three different NMDA receptor subunits have been found: NR1, NR2A/B/C/D, and NR3A/B. There are 8 different variants of the NR1 subunit and 4 different isoforms of the NR2 subunit. A ligand-binding site for glutamate is in the NR2 subunit. Other binding sites are in the NR1 and NR3A/NR3B subunits for glycine, d-serine, and d-alanine co-agonists. The overall structure of the receptor is made up of heterotetrameric complexes that contain the basic receptor subunits [40]. The most common NMDA receptor subunit combination is NR1 and NR2A [41]. Researchers have found that attachment to the co-agonist region in the receptor speeds up the opening rate of the NMDA receptor channel. This makes it easier for brain signals to send more quickly [42]. In a nutshell, both glutamate and glycine (or d-serine and d-alanine) binding are needed to make NMDA receptors work [43].

NMDA receptors are obstructed by Mg^{2+} ions during resting membrane potential [37]. Evans and Watkins looked at how glutamate receptors affect neurons in the spinal cord and found that the Mg^{2+} cation blocks the NMDA receptor very specifically. It was discovered that the Mg^{2+} cation worked even at very low concentrations (micromolar levels) and could block NMDA receptors even at physiological levels (~1 mM). After a while, these results led to the idea that Mg^{2+} ions can stop ion channels in the NMDA receptor by working without competing with them [44]. When the NMDA receptor is turned on, Mg^{2+} blockade is removed. This lets Ca^{2+} and Na^+ cations enter the post-synaptic neuron [10]. This influx of calcium ions can start signaling pathways that help cells stay alive and grow. These encompass the Phosphatidylinositol-3-kinase (PI3K)-

Table 1. Glutamate receptors and their subtypes

Glutamate Receptors						
Ionotropic Glutamate Receptors (iGluRs)				Metabotropic Glutamate Receptors (mGluRs)		
NMDA	AMPA	Kainate	Delta	Group I	Group II	Group III
NR1	GluA1	KA1	δ1	mGluR1	mGluR2	mGluR4
NR2A/B/C/D	GluA2	KA2	δ2	mGluR5	mGluR3	mGluR6
NR3A/B	GluA3	GluR5				mGluR7
	GluA4	GluR6				mGluR8
		GluR7				

NMDA: N-methyl-D-aspartate; NR: NMDA receptor; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GluA: AMPA receptor; δ: Delta receptor; KA: Kainate receptor; GluR: Glutamate Receptor; mGluR: Metabotropic glutamate receptor.

protein kinase B (AkT) pathway, the mammalian target of rapamycin (mTOR) pathway, and the release of brain-derived neurotrophic factor (BDNF) [45,46].

NMDA receptors are crucial for neuronal differentiation, synapse formation, and degradation throughout fetal development. Researchers have also found that NMDA receptors help control the movement of radial neuronal cells and some tangential neuronal cells [30]. The expression of most of the NMDA receptor subunits reaches its highest levels in the period up to 3 weeks after birth. This supports the contribution of NMDA receptors to a process that supports synaptic plasticity during this period. NMDA receptor expression, which gradually decreases after the third postnatal week, can be considered a kind of synaptic elimination mechanism [47].

NMDA receptors are also crucial in the hippocampus, facilitating the organization and retention of associative episodic memory. NMDA receptors are very important for controlling the connections that are needed to remember things and for storing evidence of what happened. The amygdala and piriform cortex both use the same receptors to control fear conditioning and the link between fear and reward. This information indicates that NMDA receptors facilitate diverse learning and memory processes in many regions of the brain [48]. Research has demonstrated that NMDA-enhancing agents potentially improve cognition and memory and positively affect quality of life [49].

AMPA Receptors

AMPA receptors are tetramers consisting of four different subunits (GluA1-4) in different combinations. AMPA receptors are low-affinity glutamate receptors that mediate much of the rapid synaptic neurotransmission that occurs in the mammalian brain. This property is also known to give AMPA receptors the potential to become inactive more rapidly than NMDA receptors. AMPA receptors have five structural compartments. A big part that is outside of cells, a part that is inside cells, a part that goes across the membrane, and agonist binding sites made up of hydrophobic and extracellular domains are these [10,30,50].

NMDA receptors are slower to excite than AMPA receptors, which are turned on by Na^+ influx [51]. It's possible for activated AMPA receptors to change where they are in the cell and how they're moving around. This can lead to LTP and LTD [30,52]. In addition, AMPA receptors activated by glutamate also activate calcium channels and trigger the mTOR signaling pathway [53].

Depolarization blockade of NMDA receptors can also be eliminated by activation of AMPA receptors. It is possible for glutamatergic neurotransmission to get stronger by activating AMPA receptors. Excitatory post-synaptic potentials (EPSPs) are in charge of rapid (EPSPs) and are an important part of learning and memory. AMPA receptors significantly contribute to the enhancement of synaptic plasticity [43].

Kainate Receptors

Kainate receptors are homomeric/heteromeric tetramers made up of five different subunits called KA1, KA2, GluR5, and GluR6. The structural skeleton of each subunit is the same. It has an extracellular amino-terminal domain, a ligand binding site, a re-entrant loop domain, three transmembrane α-helices, and an intracellular carboxy-terminal domain. KA1 and KA2 associate with GluR5-7 to form heteromeric receptors. These receptors exhibit distinct kinetic features and possess greater affinity for kainate [54]. Like AMPA receptors, kainate receptors become active when Na^+ comes in and help with fast stimulation [51]. While kainate receptors' physiological role has not been elucidated as fully as that of other glutamate receptors, it is known that they help form neuronal networks and play a part in development. It is known that the KA2 kainate receptor subunit helps synaptic circuits that support learning and memory function mature in the best way [24]. Kainate receptors' main job is to control how synapses send signals and how easily neurons can fire [55]. They fulfill these functions by contributing to synaptic plasticity in the hippocampus and sensory cortex [56]. All of these roles of kainate receptors are shown by the fact that they control neuronal networks and synaptic plasticity within the neonatal hippocampus [57].

Delta/Orphan Receptors

Despite limited knowledge on delta or "orphan" receptors, research indicates their potential involvement in synaptogenesis and synaptic plasticity [58]. Some studies in rats have identified two delta receptor subunits, δ1, which is expressed almost throughout the developing brain, and δ2, which is mainly expressed in the cerebellum. From these studies, it was seen that the δ2 subunit doesn't connect functionally with other receptor subunits, but it does play a big role in synaptic plasticity in the cerebellum [59]. Delta receptors are implicated in neurological disorders such as intellectual disability, autism spectrum disorder, cerebellar ataxia, and paraplegia. Nonetheless, limited information exists on the influence of these receptors on the progression of various disorders [30].

Metabotropic Glutamate Receptors (mGluRs)

mGluRs comprise eight subtypes categorized into three groups according to their signaling routes, pharmacological characteristics, and DNA sequence homology [60]. Group I includes mGluR1 and mGluR5, Group II consists of mGluR2 and mGluR3, while Group III include mGluR4, mGluR6, mGluR7,

and mGluR8 subunits [1]. These groups are pharmacologically, genetically, and functionally differentiated from each other [61].

mGluRs facilitate activation or inhibition processes at the cellular and molecular levels by binding ligands to G-protein-coupled second messenger systems extracellularly [1]. These receptors, which associate with guanine nucleotide-binding proteins (G proteins), release GDP upon activation by glutamate and modulate enzymes, ion channels, and vesicular transport functions [60]. All mGluR subunits/types are classified within the class C family of G protein-coupled receptors (GPCRs) and are characterized by extensive ligand-binding domains situated in the extracellular region at the N-terminus [17]. Proteins belonging to the GPCR family are composed of constitutive dimers, including mGlu receptors. The activation mechanism of mGlu receptors generally occurs in three basic steps: a) Competitive agonists bind to the venus flytrap domain (VFD) domain to close and stabilize it, b) the closed VFD transmits its signal through the cysteine-rich domain (CRD), and c) G-protein activation occurs [62].

The distribution of mGluRs depends on the receptor type: Group I mGluRs are located adjacent to synaptic dendritic spines, with mGluR5 present in the cortex and mGluR2 and mGluR3 in the hippocampus, exhibiting both pre-synaptic and post-synaptic localization in glutamatergic and GABAergic neurons. Moreover, mGluR3 is present in glial cells as well. mGluRs are common in presynaptic glutamate terminals and GABA interneurons. One of the remarkable effects of mGluR activation in the brain is that it promotes NMDAR-mediated neurotransmission [63]. Group I mGluRs specifically enhance presynaptic glutamate release, whereas Group II mGluRs diminish this release [43].

There are three groups of receptors: group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7, and mGluR8). Group II and Group III receptors are most common in presynaptic regions [61]. Group II and Group III mGluRs are mostly found at the pre-synaptic of glutaminergic, GABAergic, and neuromodulatory synapses. They also play a role in lowering cAMP levels through the inhibitory Gi/o signaling pathway [64].

Group I mGluRs

Within group I mGluR, mGluR1 and mGluR5 are generally located at postsynaptic sites that transmit/regulate downstream signaling pathways via Gq proteins and associated effectors. Receptors in this group bind to Gq/11 to activate phospholipase Cβ, and as a result of this activation, phosphoinositides are hydrolyzed to inositol triphosphate and diacylglycerol. This mechanism initiates intracellular calcium mobilization and Protein Kinase C (PKC) activation [65].

Activated group I mGlu receptors activate phospholipase D, cyclic adenosine monophosphate (cAMP) synthesis, arachidonic acid release, mitogen-activated protein kinase (MAPK) pathway, PI3K pathway, and other downstream effector molecules specific to cell type or neuronal population. In particular, activation of the MAPK/ERK pathway and mTOR/p70S6 kinase by group I mGlu receptors is recognized as crucial for synaptic plasticity processes [62]. Furthermore, G-protein-independent cascades involving Src-like protein kinases have also been identified for group I mGlu receptors [66].

LTP and LTD appear to rely on group I mGluRs similarly [62]. These receptors are usually found at postsynaptic sites. Activation of these receptors primarily stops cells from depolarizing through potassium channels. This keeps action potentials going [67]. As an example, mGluR1 makes calcium signaling better through IP3 [68], and mGluR5 changes frequency coherence at hippocampal synapses by starting somatic calcium transients [69]. According to Manzoni and Bockaert (1995), presynaptic group I mGluRs hurt postsynaptic mechanisms by blocking glutamate transmission, which could lead to LTD. Additionally, group I mGluRs on the postsynaptic side regulate neurotransmitter release on the presynaptic side by modulating endocannabinoids as backwards messengers [69,70]. It depends on protein synthesis and afferent frequency how much group I mGluRs help with persistent synaptic plasticity [62]. Some inside-cell processes and newly made proteins help make this change possible depending on how many mGluRs are turned on, and changes in frequency are a big part of figuring out which way the link between two neurons goes [71]. Additionally, the competition between mGluR5 and NMDARs may make sure that synaptic responses to afferent stimulation work both ways [72], which suggests that group I mGluRs are important for both LTP and LTD [62].

The functional roles of mGluR1 and mGluR5 receptors vary across distinct brain regions according to their specific distribution. In certain locations, these receptors coexist, whereas in others, one may predominate [73]. Group I mGluRs play critical roles in LTP induction, particularly in hippocampal CA1 neurons [17], layer V pyramidal neurons of the cortex [74] and lateral amygdaloid neurons [75]. Similarly, LTD mediated by group I mGluRs plays significant roles at synapses between neurons in the CNS [76]. mGluR1 and mGluR5 have distinct operational roles related to memory: mGluR1 is essential for information acquisition, whereas mGluR5 plays important roles in memory maintenance and spatial memory [17]. Thus, mGluR5 receptors have an important role in modulating behavioral sensitivity to psychostimulants [77]. Preclinical research shows that mGluR5 participates in forms of synaptic plasticity in medium spiny neurons (MSNs) of the nucleus accumbens (Nac) that govern cognitive acquisition and

retention mechanisms [78]. Thus, mGluR5 plays a critical role in the relationships between neuroplasticity, environmental cues, rewards, and reinforcing behaviors in MSNs [79]. Moreover, at the behavioral level, mGluR5 plays an important role in locomotor responses to novel environments, sensorimotor gating, anxiety, and cognitive functions [80].

Group II mGluRs

Although the group II mGluRs mGluR2 and mGluR3 coexist in distinct parts of the brain, mGluR3 exhibits a broader distribution compared to mGluR2. These two receptors also differ in cellular localization: mGluR2 is predominantly expressed in presynaptic nerve terminals, while mGluR3 is located in presynaptic elements, postsynaptic structures, and glial cells. Group II mGluRs function as a possible autoregulatory mechanism that protects neurons against excitotoxicity by reducing glutamate release from presynaptic terminals [43]. Elevated concentrations of mGluR2 and mGluR3 have been observed in brain regions associated with the regulation of reward and motivational mechanisms, such as the NAc, dorsal striatum, HPC (hippocampus), AMY (amygdala), PFC (prefrontal cortex), thalamus, and olfactory bulb [17]. In addition, in the human brain, mGluR3 is highly expressed in the neocortex, caudate putamen, and substantia nigra [81]. It is also known that mGluR3 is present in dendritic spines and astrocytic activity sites [82].

Group III mGluRs

The receptors included in this group are mGluR4, mGluR6, mGluR7, and mGluR8 [83]. Group III mGluRs are predominantly situated in presynaptic nerve terminals. These receptors are crucial in modulating neurotransmitter release and behavioral plasticity within the limbic circuit. Group III mGluRs exhibit an inverse relationship with adenylate cyclase-cAMP (AC-cAMP) signaling; thus, their activation at presynaptic terminals inhibits glutamate release from cortical terminals. While mGluR6 is present in the retina, the other three receptors included in this category are predominantly expressed in the CNS. mGluR4 has the highest expression level in the cerebellum, with modest expression in the olfactory bulb and thalamus [83]. mGluR7 is the most extensively expressed member of Group III mGluRs [84]. It is prominently expressed in the olfactory bulb, hippocampus, and hypothalamus. mGluR8 has a more limited expression in the CNS compared to mGluR4 and mGluR7. The most intensely expressed regions are the piriform cortex, olfactory bulb, thalamus, pons, and mammillary body [17].

EFFECTS OF GLUTAMATE AND ITS RECEPTORS ON SYNAPTIC PLASTICITY

Neuroplasticity refers to alterations in the anatomical characteristics and functions of neurons and synapses in the brain resulting from internal and external inputs. Both iGluRs and mGluRs are essential for LTP and LTD [17]. iGluRs, which are sensitive to glutamate as a ligand, are crucial for brain plasticity [85].

The equilibrium between glutamate and GABA is crucial for brain growth and development. Glutamate is an excitatory neurotransmitter, and GABA is an inhibitory neurotransmitter. Nonetheless, GABAergic neurons establish excitatory connections that transition to inhibitory as brain development progresses. It's important for synaptic plasticity and brain development and function that the excitation-inhibition (E/I) balance stays stable at neuronal synapses and neural circuits [24].

RELATIONSHIP BETWEEN GLUTAMATE AND GENDER

Functional sex differences in neurotransmitter systems in living organisms have been observed [24]. Clinical studies highlight that glutamate levels in frontal gray matter and basal ganglia (BG) are increased in women compared to men, but in parietal gray matter (PGM), men have higher glutamate concentrations than women [86]. Further research has revealed sex differences in glutamate concentrations in specific cerebral regions in more detail. For example, women have higher glutamate concentrations than men in the sensorimotor cortex, anterior cingulate cortex (ACC), striatum (STR), and cerebellum [87,88]. Conversely, glutamate concentration in the prefrontal cortex (PFC) is higher in men than in women [89]. In addition to differences in glutamate concentration in the CNS, gender-based differences in plasma glutamate levels have also been identified. Clinical studies indicate elevated glutamate levels in men compared to women, which are inversely associated with estrogen and progesterone levels [90]. Sex differences in glutamate concentrations become more pronounced with age. In particular, glutamate levels in the basal ganglia and PGM decrease with age in men, but not in women [86], whereas a more significant age-related reduction in ACC glutamate levels is observed in females [91]. Furthermore, blood glutamate levels show an age-related elevation in plasma in women, but not in males [92]. In summary, many gonadal hormones, particularly estradiol (E2), may alter the expression of sex-specific glutamate and receptors. Nevertheless, it is crucial to acknowledge that further investigation is necessary in this domain [93].

It has been suggested that gender-specific factors increase the risk of autism in men or protect women against autism because men are more affected than women. The sex-based differences in the glutamate system highlighted above underscore the necessity of comprehending the molecular processes via which glutamate malfunction may exert divergent effects on males and females [24].

GLUTAMATE RECEPTOR AGONISTS AND ANTAGONISTS

In the historical process, many substances with agonist and antagonist properties related to glutamate receptors have been identified. While some of these substances play a role in glutamatergic system pathologies, some of them lead to drugs targeted for the treatment of these pathologies. Examples of some of these substances include dextromethorphan, an approved over-the-counter cough suppressant, a non-competitive NMDA receptor antagonist, and sigma-1 receptor agonist [94]. Dextromethorphan may additionally provide therapeutic benefits through the inhibition of serotonin reuptake [95]. Dextromethorphan shows activity at receptors similar to ketamine. In vitro studies demonstrated that dextromethorphan exhibits greater NMDA receptor antagonist action than ketamine and possesses superior efficacy for sigma-1 [96]. However, dextromethorphan is rapidly metabolized by the cytochrome P450 liver enzyme CYP2D6, which prevents therapeutic plasma levels from being achieved by oral administration [96,97].

Some of the NMDA receptor antagonists approved in the market for various indications are amantadine, memantine, and acamprosate [98]. Memantine is a low to medium affinity, non-competitive NMDA receptor antagonist approved by the FDA, TPD, EMA, TGA, and the Pharmaceuticals and Medical Devices Agency of Japan (PMDA) as a symptomatic treatment for Alzheimer's disease dementia [94]. Esmethadone, a potentially novel NMDA receptor antagonist, exhibits low affinity for NMDA receptors, demonstrates ketamine-like retention within NMDA receptor channel pores, and can dissociate from the NMDA receptor when in the open configuration [99]. MIJ821 (onfasprodil) is an NMDA receptor antagonist under investigation for intravenous infusion or subcutaneous injection delivery [100]. Riluzole is a substance that can inhibit presynaptic glutamate release and engage with iGluRs [101].

When ketamine was used as a treatment, it was seen to increase pre-synaptic glutamate release and activate AMPA receptors. It turned on AMPA receptors, which then turned on more BDNF and mTOR. This started an intracellular signaling pathway that helps neurons grow [102,103]. Because of this, it was suggested that ketamine may also help treat depression [103].

Another NMDA antagonist, D-Cycloserine (DCS), is a broad-spectrum antibiotic that principally treats tuberculosis that has developed resistance to previous treatments. It is a partial agonist that can attach to the glycine site of the NMDA receptor. At doses of 100 mg/day and above, DCS works as an NMDA receptor antagonist [104].

(R,S)-3,5-dihydroxyphenylglycine (DHPG), an agonist of group I mGluRs, has been shown to elicit LTD and LTP in several brain areas [105]. CFMTI, a selective mGluR1 antagonist, can ameliorate the deficits in socialization caused by the NMDAR antagonist MK-801 in rats [106]. mGluR agonists can induce synaptic plasticity as well as intrinsic plasticity, i.e., permanent changes in membrane excitability [44].

N-acetyl-aspartyl-glutamate (NAAG) is an acetylated dipeptide present in μM-mM concentrations and selectively localized in the brain [107]. NAAG is an endogenous mGluR3 agonist that is inactivated by N-acetylated α-linked acidic dipeptidase (NAALADase) and hydrolyzed into N-acetyl-aspartate and glutamate [108]. NAAG, which exhibiting strong affinity for mGluR3 [108], and low affinity to NMDA receptors [109], can cause various reactions at pre-synaptic, post-synaptic, and extra-synaptic sites [110,111]. NAAG can exert agonistic or antagonistic effects on NMDA receptors. The factors that cause this difference may be the composition of receptor subunits or the pH level of the tissue [110–112]. Activation of NAAG is thought to reduce glutamate release [113]. NAAG is proposed to influence several diseases and conditions, including stroke, traumatic brain injury, epilepsy, age-related neurodegenerative disorders, schizophrenia, and pain, via modulating glutamate release [114].

PATHOLOGY OF THE GLUTAMATERGIC SYSTEM

Deficiencies in the expression and regulation of glutamate receptors have been linked to a variety of neuropathological conditions during development, including epilepsy, autism spectrum disorders, schizophrenia, and depression [58,115,116]. Glutamate is crucial for direct brain development and synaptogenesis [117,118], regulation of memory, behavior, and motor activities [119–121] and gastrointestinal functions [122,123] leading to glutamate-based pathologies [24]. These pathological conditions can be caused by deficits in synapse formation, excessive and abnormal glutamate signaling, and defects in the development of neural circuits, affecting both prenatal and postnatal processes. As a result, these neurodevelopmental disorders can negatively affect the lives of affected individuals in the long term [30].

There are several examples of glutamatergic system pathology. One of them is that glutamate, through NMDA and AMPA receptors, can cause cell death in seizures, cerebral ischemia, traumatic brain injury, and perinatal asphyxia. It starts the apoptosis process when the amount of Ca^{2+} inside cells goes up. This sets off enzymes such as phospholipases, proteases, endonucleases, and nitric oxide synthases [124].

mGluRs are known to be associated with schizophrenia because they modulate NMDAR-mediated neurotransmission

[60]. It has been shown that increased Ca^{2+} influx with glutamate release may lead to excitotoxicity through AMPA receptors permeable to these ions and may even cause epilepsy [125].

Other studies indicate that stress may predispose individuals to LTD in the CA1 area of the hippocampus by increasing glutamate release or inhibiting glutamate reuptake [126–129]. Both pathways have demonstrated the activation of extra-synaptic NMDA receptors, predominantly involving the NR2B subunit, in the hippocampal CA1 region of adult animals [128–131].

THE ROLE OF GLUTAMATE AND ITS RECEPTORS OUTSİDE THE CENTRAL NERVOUS SYSTEM

Research has revealed that glutamate is not only a neurotransmitter found in the brain but also plays important roles in the enteric nervous system and gastrointestinal tract [132]. In the esophagus, stomach, small intestine, and large intestine, both iGluRs and mGluRs have been found. Glutamate is thought to be present in these areas to control muscle activity and bring blood to tissues [5,123,133]. The intestine primarily obtains glutamate from food intake, with a small amount coming from microbial activity within the body. Glutamate is involved in many functions, such as taste perception and digestion [24]. Mice were given probiotics in one study, and it was seen that this increased glutamate levels in the brain and helped control metabolic activities [134,135]. In a different study, it was found that problems with the balance of dysbiotic and intestinal microbiota were linked to problems with the glutamatergic neurotransmitter system in the hippocampus tissues of mice [136]. Taking everything into account, we can say that vesicular glutamate transporters, iGluRs, and mGluRs significantly contribute to the enteric nervous system, which is not part of the central nervous system [24,29].

CONCLUSION

Glutamate is the main excitatory neurotransmitter in the central nervous system and is vital for cognitive functions, learning, and memory processes. iGluRs (NMDA, AMPA, Kainate, Delta) and mGluRs do many different things, from enabling synapses to communicate quickly to changing over time. Neurological disorders such as epilepsy, autism, schizophrenia, and depression can be associated with the glutamatergic system not working properly. On the other hand, excess glutamate can cause excitotoxicity. In conclusion, several glutamate receptor modulators appear to be a promising strategy to address the associated pathologies.

According to future research, this will help with the creation of drugs that selectively affect glutamate receptors and the discovery of neuroprotective strategies to stop excitotoxicity. In particular, personalized treatments that focus on glutamatergic dysregulations that are specific to diseases are likely to be more effective and safer ways to treat neurological and psychiatric disorders. A deeper understanding of the glutamatergic system will help create new ways to treat neurodegenerative and psychiatric disorders. It will also be an important building block for a more complete explanation of how living things work.

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