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REVIEW

A Review of Glutamate and Its Receptors: Their Roles in Brain Physiology and Pathology

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ABSTRACT

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system. Through its ionotropic and metabotropic receptors it mediates both fast transmission and long term metabolic changes in a cell. Besides neurotransmission, it takes part in development of central nervous system, cell energy metabolism and synaptic plasticity processes. Glutamatergic signaling is strictly controlled. Under normal conditions, extrasynaptic gluatamate levels are maintained at low concentrations. Excessive transmission leads to excitotoxicity which results in cell damage and death. Glutamatergic dysfunction is involved in many pathologies including neuropsychiatric, neurodegenerative and neurodevelopmental disorders. Impairments in glutamate's physiological functions, excitotoxicity and disrupted modulation of other neurotranmitter systems contribute to these pathologies. This opinion aims to summarize the cellular mechanism that lead to pathology and review how these mechanisms translate into the clinic.

Keywords: Glutamate, NMDA, Excitotoxicity, Synaptic Plasticity, Pathology

INTRODUCTION

Glutamate is the major excitatory neurotransmitter in the central nervous system. Roughly, 80-90% of the synapses in brain are glutamatergic [1]. Glutamatergic synapses are tripartite synapses. Along with the pre- and postsynaptic neurons, astrocytes actively take a part in neurotransmission [2]. Glutamate receptors are divided into two main groups, as ionotropic and metabotropic [3]. Ionotropic glutamate receptors (iGluR) are ligand-gated ion channels, consisting of 4 subunits [1]. They mediate fast excitatory synaptic transmission [4]. They are further divided into three sub-groups that differ in pharmacological and electrophysicological properties [1]. These receptors are named after their selective agonists as; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate (KA) and N-methyl-D-aspartate (NMDA) [5]. Each subunit of these receptor sub-groups may be encoded by distinct genes. In line with this, AMPA, KA and NMDA receptors may consist of combinations of different subunits as GluA1-4; GluK1-5; GluN1, 2A-D and 3A-B, respectively [1]. Subunit composition of receptors vary in different brain regions [3]. Morevover, in the course of physiologic (i.e. aging), and pathologic processes subunit expressions may change[6-8]. NMDA receptors are structurally more complex than AMPA and KA receptors. Alongside with the glutamate, there exist; binding domains for co-agonists, glycine and D-serine and allosteric modulators, Zn^{+2} and polyamines [9]. NMDARs are blocked by Mg^{+2} in a voltage-dependent manner and at resting membrane potentials the channel is in closed state [4]. NMDA receptors are permeable to Na^{+} and K^{+} as AMPA and KA receptors, however they are more permeable to Ca^{+2} than other sub-groups [1,9]. NMDAR activation requires; concurrent

binding of glutamate and glycine or D-serine, and removal of Mg^{+2} blockage by postsynaptic membran depolarization [1]. Metabotropic glutamate receptors (mGluR) are from family of G protein coupled receptors and coupled to downstream signaling cascades that act on much slower timescales [4]. There are 8 different mGlu receptors identified. Based on their aminoacid sequences, pharmacological characteristics and intra-cellular signaling pathways, these receptors are grouped into 3 classes [10]. Group I mGlu receptors (mGlu1, mGlu5) are coupled with Gq protein [1]. Ligand binding to these receptors leads to phospholipase C (PLC) stimulation, and subsequent activation intracellular signaling pathways which are mediated by inositol-3-phosphate (IP3) and diacylglycerol (DAG). Group II (mGlu2, mGlu3) and III mGlu (mGlu4, mGlu6, mGlu8, mGlu7) receptors are Gi protein coupled [1]. Activation of these receptors inhibits adenylate cyclase enzyme activity, and as a consequence cAMP mediated signaling pathways. Typically, Group I mGluRs are located postsynaptically, whereas Group II and III mGluRs are presynaptic, and also present on astrocytes [11]. Distribution patterns of these receptors also differ, such that, in spesific brain regions, certain sub-groups are expressed more frequently [10]. In the cell, glutamate is found to be concentrated in synaptic vesicles, and accumulation is mediated by vesicular glutamate transporters (VGLUTs) [1]. Normally, in relative to intracellular compartment, extracellular gluatamate levels are kept low, and this is maintained via synaptic and/or extrasynaptic excitatory aminoacid transporters (EAATs) [12]. EAATs remove glutamate from the extracellular space. In the mammals there are 5 type of EAATs identified. EAAT 1 and 2 are expressed on astrocytes and EAAT 3 on neurons [5].

Glutamatergic system takes part in maintaining the normal brain function, cognitive functions such as learning and memory, and also neurodevelopmental processes. Accordingly, glutamatergic system dysregulation is involved in many psychiatric and neurodegenerative diseases. In the first part of this review, cellular mechanisms of physicologic and pathologic events where glutamatergic system plays a role will be outlined, then their manifestations in clinic will be discussed.

Cellular mechanisms

Cellular Energy Metabolism

In the neurons, glutamate is synthesized from α-ketoglutarate by addition of an amino group to the molecule. α-ketoglutarate is one of the intermediates formed during Krebs cycle. Glutamate in the synaptic cleft is taken up by glia. Here, in the glia, glutamate reacts with free ammonia, resulting in glutamine synthesis. Glutamine is released from glia to extracellular space and taken up by neurons. In the neurons, glutamine is converted back to glutamate by glutaminase. This metabolic pathway between neurons and glia is called glutamate-glutamine cycle. Glutamate-glutamine conversion in the neurons is of importance with regard to cellular energy metabolism. Some part of newly formed glutamate is converted to α-ketoglutarate by glutamate dehydrogenase. In this way Krebs cycle and energy production are sustained [1]. Moreover, it was suggested that; glutamate presence in astrocytes causes a shift in energy production mechanisms from oxidative metobolism to glycolysis, and then, lactate -the end-product of glycolysis- is used by neurons as a substrate for oxidative phosphorylation [13]. Glutamate may also play an important role in nitrogen homeostasis. There is evidence that glutamate acts as a nitrogen buffer during α-ketoglutarate and glutamine conversions, and this is applicable for both normal and hyperammonemic conditions [14].

Neurogenesis

Neuronal cells, astrocytes and oligodendrocytces originate from embryonic progenitor cells. Progenitor cells continue to exist in some regions of postnatal and adult brain and found to be involved in neurogenesis during these periods [15]. It was reported that glutamate receptors expressed on progenitor cells; moreover proliferation, migration and differentiaton of the cells are modulated by glutamatergic system. In line with this, AMPA/KA, NMDA and mGlu5 receptors were shown to mediate neurogenesis during embryonic stage, after birth and adulthood [15-17].

A recent study investigated the glutamate receptors in various regions of Wistar rat brains of different age groups by using quantitative *in vitro* receptor autoradiography [18]. AMPA receptor

densities were significantly higher ($p < 0.01$) in P90 rats compared to P0 in all brain regions investigated (olfactory bulb: 262%; striatum: 311%; hippocampus: 321% and cerebellum: 471%). Although the course of changes between age groups was comparable in all examined areas, their peak varied for the different brain regions. Between P0 and P10, a significant increase was found in the olfactory bulb, the striatum and the hippocampus, but not in the cerebellum. Significant changes were found between P10 and P20 only in the cerebellum and between P20 and P30 in the striatum and cerebellum. KA receptor densities were significantly higher in P90 rats compared to P0 in all brain regions investigated including olfactory bulb, striatum, hippocampus and cerebellum. Between P0 and P10, densities increased significantly in the olfactory bulb, striatum and hippocampus. Furthermore, between P10 and P20, a significant increase was found only in the striatum and cerebellum, whereas no significant changes were found between P20 and P30. Interestingly, between P30 and P90, there was a decrease in receptor densities, though it only reached significance in the striatum. NMDA receptor densities were below the detection limit in the brain of P0 rats and in the cerebellum at all ages. In the olfactory bulb, NMDA receptor densities were higher at P90 than P10, whereas the opposite was true for the striatum and hippocampus. Between P10 and P20, NMDA receptor densities increased significantly in the hippocampus. No significant changes were found between P20 and P30. Between P30 and P90, a significant decrease was found in the striatum and hippocampus [18]. The analysis of mRNA expression levels of NMDA receptor subunits revealed NR2B expression predominately in the first postnatal week, and NR2A expression in the following weeks [19-21]. This subunit switch is thought to play a developmental role in NMDA neurotoxicity [22] and indicates the importance of neonatal neurotransmission mediated by the NMDA receptor[19]. During synaptogenesis, there is an increase in the numbers of synapses until reaching its peak after P28, but the numbers then decline slowly during maturation, a process known as synapse elimination [23,24]. Hence, the decline of receptor densities in striatum and hippocampus from P30 to P90 may be due to synapse elimination to redefine or rather fine-tune neuronal networks. Moreover, NMDA receptor activation results in the insertion of AMPA receptors and alters dendritic spine morphology, which is important for the stability and maturation of synapses [25].

Modulation of Synaptic Transmission

mGlu receptors change activity of voltage and ligand gated ion channels via intracellular signaling pathways of which they are coupled with. Each of three sub-groups inhibits L-type voltage-gated Ca^{+2} channels, group I and II receptors also inhibit N-type voltage-gated Ca^{+2} channels [1]. Besides, they alter excitability of the cell by regulating the activity of various K^{+} channels [9]. On the postsyanptic neurons, activation of mGluR, modulates ligand-gated receptors such as; NMDA, KA, GABAA. The context of this modulation may vary and may be ion channel activation or inhibition in different tissues [1]. Group II and III mGluRs on the presynaptic neurons function as autoreceptors. It has been shown that their activation inhibits neurotransmitter release from glutamatergic, GABAergic and monoaminergic neurons [26].

Synaptic Plasticity

Synaptic plasticity, very broadly, can be defined as strengthening and/or weakening of synaptic connections between neurons. In terms of functionality, it primarily serves to learning and memory processes. Moreover, it has been shown that it plays a crucial role in development of neural circuits. It has been observed in many brain regions and there are multiple types of it. Long term potentiation (LTP) and long term depression (LTD) are two types of synaptic plasticity, of which studied the most [27].

At the molecular and cellular level, it was observed that LTP occurs via different mechanisms in distinct circuits of the same tissue [28]. LTP in Schaffer collaterals of the hippocampus is mediated by NMDA and AMPA receptors.

During the induction phase of LTP, a sequence of events occurs as follows; postsynaptic AMPAR activation, postsynaptic neuron depolarization, removal of Mg^{+2} blockage from NMDAR, increased Ca^{+2} influx into the postsynaptic neuron and finally activation of Ca^{+2} dependent kinases. Next, AMPARs in the synaptic pool are inserted to the membrane, meanwhile, protein kinase C induction increases

AMPAR permeability. Collectively, increased number of AMPARs and their permeability enhance synaptic transmission efficacy.

It was shown that, NMDA and AMPA receptors in Schaffer collaterals also features in LTD [28]. In this form of synaptic plasticity, unlike in LTP, synaptic efficacy is decreased. This is achieved by stimulating postsynaptic neurons at low frequencies for extended time periods. As a result of low frequency stimulation, postsynaptic neuron is less depolarized and Ca^{+2} influx to the neuron is lower when compared to LTP activity [27]. Ca^{+2} at low concentrations activates calcium-dependent phosphatase calcineurin, which has a highger affinity to Ca^{+2} than CaMKII. Calcineurin dephosphorlyates and phosphorlyates AMPAR subunits, GluR1 and GluR2, respectively, which results in AMPAR endocytosis [28].

Besides iGluRs, mGluRs are also involved in LTD. Underlying mechanisms of mGluR mediated LTD is not clear yet. Still, there are several pathways and gene transcription products which were proposed as mediators of AMPAR internalization [29]. In this context, MAPK and mTOR pathways are especially thought to be important for mGluR mediated synaptic plasticity [26].

It is likely that, apart from hippocampus, glutamatergic sytem participates in synaptic plasticity in basal ganglia as well. It was observed that NMDAR activity here alters LTP, LTD and striatal learning performance by modulating the dopaminergic system [30,31].

Excitotoxicity

Excessive glutamatergic transmission disrupts normal cellular functions by triggering a set of events in the cell. These events are often interrelated, they cause neural damage and death, and the process is called excitotoxicity. Excitotoxicty usually occurs when extracellular glutamate levels are high. However, in hypoxic and hypoglycemic conditions, where cellular homeostasis is impaired, even non-toxic glutamate levels are detrimental [32]. In most of the excitotoxic events, Ca^{+2} is involved. Extracellular glutamate increases intracellular Ca^{+2} by binding to AMPA, NMDA and group I mGlu receptors. In the cell, Ca^{+2} activates several enzymes such as proteases, phospholipases and endonucleases [33]. These enzymes induce multiple events including; mitochondrial damage, lipid peroxidation, increase in reactive oxygen species, DNA damage, endoplasmic reticulum dysfunction and acidosis [9]. As a result, cell undergo apoptosis and/or necrosis. Pathological conditions also cause glutamate transporter dysfunctioning. Impaired re-uptake of extrasynaptic/nonsynaptic glutamate to the cells and/or glia is another factor that contributes to excitotoxicty [9,32].

Clinical Pathologies

Migraine

There is increasing evidence indicating a role for glutamate in migraine. Levels of glutamate are higher in the brain and possibly also in the peripheral circulation in migraine patients, particularly during attacks [34]. Population based genetic studies point genes that are involved with glutamate signaling in migraine, and gene mutations responsible for familial hemiplegic migraine and other familial migraine syndromes may influence glutamate signaling. Animal studies indicate that glutamate plays a key role in pain transmission, central sensitization, and cortical spreading depression. Multiple therapies that target glutamate receptors including magnesium, topiramate, memantine, and ketamine have been reported to have efficacy in the treatment of migraine [34].

A recent study shows the first direct support of a threshold level of extracellular glutamate for spreading depolarization (SD), that is electrophysiological corralate of migraine aura, ignition regardless of genotype [35]. This study defines a new glutamatergic release mechanism which is called glutamatergic plumes. Plumes are non-canonical, calcium-dependent glutamate signaling events, driven by both astrocytic glutamate clearance impairment and neuronal action-potential-independent release that occur spontaneously in the FHM2 model of migraine with aura and in wild type mouse brain [35]. The prediction of the model is that increased susceptibility to SD in both FHM1 and FHM2 [36,37] is due to the fact that the glutamate threshold is reached with stimuli of lower intensity. Given that impaired glutamate clearance primarily affects the activation of NMDA receptors [38,39]. This study suggests a possible role of plumes in the cooperative activation of NMDA receptors necessary for SD ignition [35].

The association of plumes with SD and with experimental conditions relevant to neuronal injury proposes that plumes may represent a broadly relevant mechanism of neurological disease.

Epilepsy

Epilepsy is a chronic disease characterized by spontaneous and recurrent seizures. Epileptic seizures result from overstimulation and synchronized discharge of neurons. Spontaneous and recurrent seizures develop gradually over time as neuronal networks become more excitable, and this process is called epileptogenesis [40].

Epileptic seizures represent increased glutamatergic and decreased GABAergic transmission. NMDAR and AMPAR agonists induce epileptic seizures both in animals and humans [41]. Besides, in patients with epilepsy, elevated glutamate levels during post-ictal phase have been shown *in vivo* in many studies [5]. Excess glutamate in extracellular compartment, which enhances synaptic efficacy, is viewed as a contributor to epileptogenesis. On that note, activation of AMPAR and NMDAR, that are both involved synaptic plasticity, becomes prominent. Mutations in NMDARs and, to a lesser extent in AMPARs, were reported to be linked to epilepsy [41]. In epilepsy models, it was observed that number of NMDARs was increased, presynaptic mGlu2/3 receptors was decreased and GABARs were internalized following *status epilepticus* [7]. As a result of these events, which enchance glutamatergic signaling and release, it is likely that cells becomes more excitable. Within this context, glutamate re-uptake mechanisms are also under consideration. It was reported that number of glial transporters declined in both patients and animal models of the disease [7]. Another part for glia in the pathology, may be related to their role in glutamate and cell energy metabolism. It was proposed that, astrocytic dysfunction leads to increse in extracellular glutamate levels and cell excitability, as a result of disrupted glutamate-glutamine cycle [42].

Antiepileptic drugs used today act on glutamatergic system either directly or indirectly. However, 30% percent of the cases is resistant to treatment. With agents that modulate neuron-glia interaction and cell energy metabolism, it seems possible to make progress within this treatment-resistant population.

Alzheimer's Disease

The pathophysiology of Alzheimer's disease (AD) is highly complex. Several processes such as; formation amyloid ß (Aß) peptide and Tau protein, mitochondrial damage, oxidative stress, inflammation, cholinergic dysfunction are known to be involved in the pathology. Among others, Aß peptide formation is one of the main contributors to the disease development, and found to cause glutamatergic system dysfunction. Previous stuides report that Aß peptides disrupt glial EAAT2 functioning [12], alter the expression of presynaptic proteins which take part in neurotransmitter release, and directly enhance NMDAR mediated synaptic transmission and elevate D-serine levels [31]. It was also proposed that, in AD, astrocytic glutamate levels and extrasynaptic NMDAR activity are increased [31,43]. Available data supports the idea that increased glutamatergic signaling mediate excitotoxicty and neurodegeneration in AD [3].

Parkinson's Disease

In Parkinson's disease, primary pathology is degeneration of nigrastriatal dopaminergic neurons and subsequent depletion of striatal dopamine. Secondary to the dopaminergic deficit, glutamatergic dysfunction is thought to be implicated in motor impairments and progressive neurodegeneration [44,45]. Results from animal studies indicate that, in the basal ganglia, subunit compositon and expression of iGlu and mGlu receptors are altered [8]. Moreover, gluatamatergic activity is increased [10]. When combined with dopaminergic agents, NMDAR and AMPAR antogonists have been found to be beneficial to improve motor functions and Levodopa induced dyskinesias (LIDs)[8]. NMDAR antagonist amantadine is currently in clinical use for LIDs. It was also suggested that mGluR modulation might be an effective treatment modality for LIDs, as well as provide neuroprotection [8,46]. Within this scope, several agents from group I mGluR antagonists, negative allosteric modulators, group II and III agonists, positive allosteric modulators have been tested preclinically and results have been promising [10].

Huntington's Disease

Huntington's disease (HD) is a genetic disorder that is mostly inherited. It manifests with motor

impairments -chorea being the most dominant- and accompanying psychiatric and cognitive symptoms [10]. In HD, key pathalogical finding is degeneration of cortical neurons and basal ganglia. Dopaminergic and glutamatergic imbalance is thought to be implicated in chorea [47]. It is also likely that, as in other neurodegenerative diseases, glutamate excitotoxicity elicit neuronal death. It was shown both in animal models and HD patients that glutamate transporter GLT-1/EAAT2 expression is reduced [48]. In line with this, agents that decrease glutamate release via mGluR2/3 activation are suggested to be as candidate drugs for treatment [10].

Ischemic Stroke

Glutamatergic system is directly related to neuronal death after stroke. In ischemic tissues, energy homeostasis is disrupted. Hypoxic conditions cause activation of voltage gated Ca^{+2} channels on the presynaptic neuron, and reverse sodium-calcium exchange both in neurons and astrocytes [3,49]. Increased Ca^{+2} in the cell triggers glutamate release. It was also reported that; under ischemic conditions, neuronal and glial glutamate transporters operate in the reverse mode and/or their expression levels are reduced [5,49]. For the treatment of stroke; NMDAR antagonists, which reduce increased glutamatergic signaling and prevent subsequent excitotoxicity, were found to be successful in animal studies, but failed in clinical trials [50]. However, by targeting the intracellular processes which follow NMDAR activation and provoke cell death, it seems possible to obtain more favorable results for the treatment.

Neurodevelopmental Disorders

Neurodevelopmental disorders are a cluster of conditions that include autism, attention deficit/ hyperactivity disorder, Down syndrome, Rett syndrome, Fragile X syndrome and mental retardation. They are primarily related developmental anamolies of central nervous system and characterized by motor, cognitive and emotional symptoms.

In the recent studies, it was reported that disrupted formation of glutamatergic synapses might have a role in neurodevelopmental impairments, hence glutamatergic dysfunction was suggested as a common underlying mechanism in these disorders. Mutations were shown in genes encoding AMPA, NMDA, mGlu receptors and postsynaptic density proteins [51]. Biochemical and post-mortem analysis revealed elevated glutamate levels in patients with autism [52,53]. The reason for this increase was suggested to be disrupted glutamate/ glutamine metabolism as a result of gliolisis and decline in glutamate decarboxylase enzyme [52]. Further, in clinical trials, autism symptoms improved with glutamate antogonists memantine and amantadine [53].

Similarly to autism, glial cells are thought to be implicated in attention deficit/hyperactivity disorder (ADHD). It was shown that, neuroinflammatory responses that was controlled by glial cells and also extracellular glutamate levels were altered in ADHD [54]. Modulatory effect of glutamatergic system on dopaminergic neurons is a proposed mechanism as a contributor to ADHD pathology [55].

Depression

Major depression is a serious health condition, and is quite common on a global scale. According to latest WHO data, it affects more than 260 million people worldwide [56].

Known mechanisms underlying depression are varios and rather complex. As well as neurochemical and immunological impairments, genetic susceptibility end enviromental factors are major contributors to the etiology [57]. Monoamine hypothesis, that was proposed in 1950s, predicts an imbalance between serotonin, noradrenaline and dopamine levels in the brain [58]. Many medications used today are developed on the basis of this theory. Even so, there are limitations to monoamine hypothesis and it does not account for the disease pathophysiology alone [59].

In early 2000s, upon the observations that NMDAR antagonist ketamine has acute antidepressant effects, the connection between glutamatergic system and depression became a popular topic for researchers. In the studies conducted on patients with depression; serum/plasma glutamate and cerebrospinal fluid glutamine levels were reported to be increased [5,58], gluatamate in prefrontal cortex and anterior cingulate cortex were shown to be decreased[60]. Glial reduction was also observed and this was suggested to be related to glutamate excitotoxicty [5,58]. Moreover, in post mortem

studies, variations have been reported in NMDA and AMPA subunit expressions for individuals with unipolar and bipolar disorders [5,11,60]. These data indicate a strong relationship between depression and glutamatergic dysfunction. Besides, elucidation of ketamine's mechanism of action in depression, contributed to a better understanding of the disease pathophysiology at the molecular level. Ketamine antagonizes NMDARs on GABAergic interneuros, thus increases glutamate release. Subsequent to gluamate increase, intracellular Ca^{+2} are elevated by postsynaptic NMDARs and AMPARs activation, and BDNF release is triggered [58,59]. BDNF enhances mTORC1 signaling via ERK-AKT pathway. mTOR pathway activation induces intracellular protein synthesis such as BDNF, GluA1 and PSD95 [11]. In addition, it was reported that ketamine blocks extrasynaptic NMDA receptors on the postsynaptic cell. Net effect of this action is disinhibition of eEF2 and increased synthesis of BDNF and synaptic proteins [11]. These data support the involvement of synaptic plasticity and glutamatergic system in depression. In line with the ketamine's effects on NMDAR and AMPAR, there are several NMDAR antagonists and AMPAR positive allosteric modulators in development as candidate therapeutics. Less data are available in regard to metabotropic receptors, however it was shown in preclinical studies that mGluR2/3 and mGluR5 antogonists possess ketamine-like effects [61,62].

Anxiety Disorders

Anxiety disorders are often co-occur with depression. In the treatment, serotonine reuptake inhibitors and benzodiazapeines are commonly used. Current treatment approaches are successful ameloriating the symptoms, still there is a need for superior treatments in terms of efficacy and side effect profile [63]. Neural substrate for the stress response is corticolimbic circuits, that includes GABAergic, dopaminergic and serotoninergic systems. It is known that, being the major exciatatory neurotransmitter, glutamate modulates these systems.

Since depression and anxiety are concomitant diseases, and known underlying mechanisms overlap to some degree, it is possible that glutamatergic system is also involved in anxiety. In precilinical studies, it was observed that; acute stress increases glutamate in prefrontal cortex and limbic structures, whereas chronic stress downregulates glutamate receptors and decreases transmission efficacy [64]. Data from human imaging studies are inconsistent. Still it was reported that gluatamate levels in prefrontal cortex were elevated [64], and gluatamate/creatinine ratio in anterior cingulate cortex correlated with anxiety scores [5]. Within this context, agents that target glutamatergic system and act via different mechanisms were tested in animal and human studies. NMDAR antagonists ketamine and memantine, NMDA partial agonist D-cycloserine, glial cystine-gluatamate transporter modulator N-acetylcysteine, voltage gated Ca^{+2} channel blocker riluzole are some of them [63,64]. In these studies, drugs that decreases glutamatergic transmission showed anxiolytic effects. Yet, these were open label clinical studies conducted with small-size populations. For the use of glutamatergic agents as therapeutics, evidence from larger population-based randomized controlled studies is needed.

Obssessive compulsive disorder (OCD) is aetiologically known to be linked to dysfunction of cortico-striatal-thalamic circuit. Studies indicate that glutamatergic signaling might be involved in dysfunctioning of these pathways [5,63,64]. It is not clear yet how different glutamate receptors are implicated in the disease pathophysiology. In clinical trials glutamate antagonists; memantine, ketamine, topiramate and glutamate release inhibitors such as riluzole and lamotrigine have been tested [65]. But, as in anxiety studies, results obtained are not consistent and more studies with larger sample sizes should be conducted.

Schizophrenia

Schizophrenia is a serious psychiatric disorder, characterized by positive (hallucinations, delusions, disorganized thinking), negative (affective impairment, anhedonia, antisocial behaviour) and cognitive (attention deficit, learning and memory impairments) symptoms [66]. It is a multifaceted illness that has genetic, enviromental and prenatal risk factors.

The very first theory relating to underlying disease mechanism is dopamine hypothesis. It states that, in schizophrenia, activity of mesolimbic dopaminergic pathway is increased [67]. The hyptohesis is proved to be true many times with pre-clinical and clinical data, however it falls short on explaining some other aspects of the disease. In line with the latest

available data, it is now known that, serotonine and glutamate play a role in disease pathophysiology. Glutamatergic dysfunction is considered to be a better model for explaining the negative and cognitive symptoms [68]. Moreover, it was suggested that all three systems, dopaminergic, serotoninergic and glutamatergic, are linked to psychosis [69].

The glutamate hypothesis of schizophrenia emerges from the discovery that NMDAR antagonists phencyclidine and ketamine cause schizophrenia-like symptoms [70]. According to this theory, in schizophrenia, NMDARs on cortical GABAergic interneurons are hypofunctional. Net effect of this hypofunctionality is disinhibiton of interneurons, elevated glutamate levels and increased glutamatergic transmission [68]. Glutamatergic dysfunction was shown in animal studies and in humans with *in vivo* imaging techniques [66,68,70]. In genetic studies, risk allells linked to certain GluR subunits have been identified, and also variations in receptor subunit expression have been reported in post-mortem studies [66]. In clinical studies, several drugs that modulate NMDAR activity or glutamate release have been tested, but none of them found to be effective as much as dopamine receptor blockers [70].

It is worth noting that there is an extensive interaction between dopaminergic and glutamatergic systems. Thus, for the design of future studies, it seems as a better approach to consider the relationship between glutamate and dopamine.

CONCLUSION

Glutamate is a unique neurotransmitter in terms of its functionality. It excites almost every neuron in the brain. Along with signal transmission, it has a part in many key processes such as; central nervous system development during prenatal period, maintanance of cell homeostasis and synaptic plasticity. Glutamatergic signaling is essential to sustain vital functions, however excess signaling results in cell death. Since the glutamate is found widespread and features in critical events in the brain, glutamatergic system dysregulation contributes to pathophysiology of several diseases. Known mechanisms of neuropsychiatric, neurodegenerative and neurodevelopmental disorders are complex and multifactorial, still, in all cases, signal transduction and cell energy metabolism are disrupted. Synaptic plasticity and excitotoxicity are more prominent for some of these diseases, and these topics could be of great interest for further research.

Abbreviations

Aß	Amyloid Beta
AD	Alzheimer's Disease
ADHD	Attention Deficit/Hyperactivity Disorder
AKT	v-Akt Murine Thymoma Viral Oncogene
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPAR	AMPA Receptor
BDNF	Brain Derived Neutrophic Factor
cAMP	Cyclic AMP
DAG	Diacylglycerol
EAAT	Extrasynaptic Excitatory Aminoacid Transporter
eEF2	Eukaryotic Elongation Factor 2
ERK	Extracellular-regulated Kinase
FHM1	Familial Hemiplegic Migraine 1
FHM2	Familial Hemiplegic Migraine 2
GLT	Glutamate Transporter
GABA	Gama Amino Butiric Acid
HD	Huntington's Disease
iGluR	Ionotropic Glutamate Receptor
IP3	Inositol-3-phosphate
KA	Kainate
LID	Levodopa Induced Dyskinesia
LTD	Long Term Depression
LTP	Long Term Potentiation
MAPK	Mitogen Activated Protein Kinase
mGluR	Metabotropic Glutamate Receptors
mTOR	Mammalian Target of Rapamaycin
mTORC1	Mammalian Target of Rapamycin Complex 1
NMDA	N-methyl-D-aspartate
NMDAR	NMDA Receptor
PD	Parkinson's Disease
PLC	Phospholipase C
PSD95	Postsynaptic Density Protein 95
SD	Spreading Depolarization
OCD	Obssessive Compulsive Disorder
VGLUT	Vesicular Glutamate Transporter
WHO	World Health Organization

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Conflict of interest

The authors declare that there is no conflict of interest.

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