Glutamate Neurotoxicity in ALS and Epilepsy

Hisham Ahmed
Faculty of Veterinary Medicine, Cairo University

Glutamate plays a crucial role in brain activity as the primary excitatory neurotransmitter in the mammalian central nervous system. However, it could be a profoundly serious endogenous toxin if any disruption happens in its concentration or function. Glutamate dyshomeostatic effects can range from the induction of neuron death to neural circuit modification. This review will cover the research connecting glutamate neurotransmission, the development of amyotrophic lateral sclerosis (ALS), and epilepsy. It will concentrate on the molecular processes that control glutamate concentration and activity, and how these systems are disrupted in ALS and epilepsy. These molecular processes offer molecular targets that could help to develop novel therapeutic agents.

Abbreviations: ADAR2 – Adenosine deaminase acting on RNA 2; ALS – Amyotrophic lateral sclerosis; AMPAR – Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic acid receptors; EATT2 – Excitatory amino acid transporter; FMRP – Fragile X mental retardation protein; mGluR – Metabotropic glutamate receptors; NMDA – N-methyl-D-aspartate; TDP-43 – Tar DNA-binding protein 43; TLE – Temporal lobe epilepsy; VGLUT – Vesicular glutamate transporter.

Keywords: Glutamate excitotoxicity; Amyotrophic lateral sclerosis; Epilepsy

Introduction

Under physiological conditions, glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. Its pivotal role extends to brain development, synaptic plasticity, learning, and memory (Mattson, 2008). Glutamate exerts its function through glutamate receptors, which can be categorized into ionotropic glutamate receptors—comprising ligand-gated ion channels, such as N-methyl-D-aspartic acid receptors (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), and kainate receptors—and metabotropic glutamate receptors (mGluRs), which fall under the class of G-protein coupled receptors. Notably, intracellular glutamate concentrations are maintained at millimolar levels, while extracellular concentrations reside in the micromolar range (Featherstone and Shippy, 2008). This delicate balance of extracellular concentration is adjusted by neurons and glial cells through regulation mechanisms involved in glutamate release and reuptake. Disruption in these finely tuned regulation mechanisms of glutamate release and reuptake can lead to elevation of extracellular glutamate (Lewerenz and Maher, 2015). This disruption has been linked to neuronal damage in multiple acute neurological disorders, such as ischemia and traumatic brain injury. However, it has also been linked to chronic neurological disorders including ALS, Parkinson's disease, Alzheimer's disease, epilepsy, and Huntington's disease (Dong et al., 2009).

Excess extracellular glutamate can induce neuron death. Lucas and Newhouse were the first to document glutamate's toxicity, describing degeneration of the inner layers of the retina in infant mice after subcutaneous glutamate injections (Lucas and Newhouse, 1957). In a landmark paper in 1969 the term “excitotoxicity” was established by Olney, who showed that a high glutamate level could induce a brain lesion in several regions of the developing brain including the hypothalamus (Olney, 1969). This early recognition of glutamate's harmful effects laid the foundation for understanding its
role in neuronal damage. Furthermore, glutamate excitotoxicity can contribute to the reshaping of neural circuitry within neuronal networks—an effect that can underlie network hyperexcitability (Sun et al., 2001; Barker-Haliski and White, 2015). Therefore, it becomes evident that the consequences of glutamate excitotoxicity span a wide spectrum, ranging from single-neuron death to structural modifications within neural circuits. To illustrate this wide-ranging impact, this review focuses on the context of two specific neurological disorders, ALS and epilepsy. It will focus on the molecular mechanisms responsible for regulation of glutamate concentration and function and how these mechanisms are disrupted during ALS and epilepsy. These molecular insights offer an opportunity to modulate glutamatergic signaling at a molecular level, providing novel therapeutic targets.

Excitotoxicity and ALS

ALS is a neurodegenerative disease that is characterized by the degeneration of upper and lower motor neurons leading to motor symptoms. This degeneration of motor neurons results in a progressive weakening of respiratory and limb muscles and leads to the death of the patients usually 2 to 5 years after the diagnosis (Mejzini et al., 2019). ALS has an estimated incidence of 1.75–3 per 100,000 persons per year and a prevalence of 10–12 per 100,000 in Europe (Masrori and Damme, 2020). Glutamate excitotoxicity is thought to have a key role in the progression of ALS. Cortical hyperexcitability has been observed in individuals with sporadic ALS and familial ALS with superoxide dismutase 1 (SOD1) mutation, with familial ALS showing hyperexcitability even before the onset of symptoms (Vucic et al., 2008). Glutamate could be behind such hyperexcitability, as it can be alleviated by using riluzole, which is a glutamate antagonist (Stefan et al., 2001). This hyperexcitability in corticomotor neurons has been hypothesized to be the reason behind the degeneration of anterior motor horn cells via an anterograde glutamate excitotoxic process (Eisen et al., 1992). Hypoglossal motor neurons in neonatal transgenic mice with SOD1$^{G93A}$ mutation exhibited hyperexcitability two to three months before motor neuron degeneration and clinical symptoms occurred, indicating that hyperexcitability isn’t a compensatory mechanism but a primary change (Zundert et al., 2008). Glutamate levels increase in the blood of ALS patients (Kumar et al., 2010). Additionally, there is a significant rise in glutamate levels in the cerebrospinal fluid (CSF) of ALS patients (Rothstein et al., 1990).

AMPA receptors

AMPA receptors are important glutamate receptors in the brain and spinal cord. They consist of four subunits GluA1, GluA2, GluA3, and GluA4 (Traynelis et al., 2010). AMPAR have been linked to ALS because excessive calcium influx through AMPAR drives motor neuron death (Carriedo et al., 1996). Furthermore, AMPAR are two to three times more abundant in motor neurons than in dorsal horn neurons, and motor neurons exhibit a low level of calcium-binding protein (Vandenberghe et al., 2000; Leal and Gomes, 2015). Calcium permeability via AMPAR is mediated by the lack of GluA2 or impaired transcription editing at the Q/R site of mRNA of GluA2 (Tateno et al., 2004). In the same spinal cord region, the expression level of the GluA2 subunit is lower in spinal motor neurons than in dorsal horn neurons (Heath et al., 2002). In the ventral grey horn of ALS patients, there is a significant reduction in transcription editing of GluA2 compared to the control group (Takuma et al., 1999; Kawahara et al., 2004). Adenosine deaminase acting on RNA 2 (ADAR2) is responsible for GluA2 transcription editing (Hideyama and Kwak, 2011). In ALS patients' motor neurons, ADAR2 is downregulated but not ADAR1 or ADAR3 (Hideyama et al., 2012). In ADAR2 knockout mice, upregulation of ADAR2 in motor neurons rescued these neurons (Yamashita et al., 2013). Furthermore, compared to the control group, ALS patients exhibit lower ADAR2 expression in motor neurons, and ADAR2 was found to be implicated in the aggregation of Tar DNA-binding protein 43 (TDP-43) in motor neurons, which is the most significant hallmark in ALS pathology (Aizawa et al., 2010; Yamashita and Kwak, 2019). Expression of the edited GluA2
subunit in spinal motor neurons has been found to slow the progression of ALS and reduce mortality (Tateno et al., 2004). Notably, motor neurons with the familial ALS mutation C9ORF72 demonstrate increased expression of the GluA1 subunit, resulting in higher levels of calcium-permeable AMPAR and increased susceptibility to excitotoxicity. These alterations were not observed in induced pluripotent stem cell-derived cortical neurons and could be reversed through CRISPR/Cas9-mediated correction of the C9ORF72 mutation (Selvaraj et al., 2018). The SOD1^{G93A} mutation in astrocytes causes GluA2 subunit regulation in motor neurons to be disrupted, rendering them more vulnerable to excitotoxicity (Damme et al., 2007). In conclusion, evidence implies that increased AMPAR distribution and defective expression of GluA2 subunit or improper transcription editing at Q/R site in AMPAR leads to the accumulation of calcium ions inside motor neurons and subsequently increased vulnerability to excitotoxicity.

**Excitatory amino acid transporter**

The impairment of glutamate transport is also linked to the development of ALS. Glutamate uptake is mediated in physiological settings by excitatory amino acid transporter (EAAT), which is primarily expressed in astrocytes (Hardiman et al., 2017). Loss of EAAT2/GLT-1 expression causes glutamate buildup and motor neuron death in vivo and in vitro experiments (Rothstein et al., 1996). Glutamate uptake was found to be reduced in autopsied spinal cord of ALS patients (Rothstein et al., 1992). EAAT2/GLT-1 detection is reduced in ALS patients, particularly in spinal cord regions with significant motor neuron loss, while EAAT1/GLAST remains unaffected (Sasaki et al., 2000). During the symptomatic stage, EAAT2/GLT-1 is reduced in transgenic mice carrying the SOD1^{G93A} mutation. Another study found EAAT2/GLT-1 to be reduced during the presymptomatic stage in transgenic rat carrying the same mutation (Bendotti et al., 2001; Howland et al., 2002). In SOD1^{G93A} mice, the activation of EAAT2/GLT-1 translation by small compounds prevents motor neuron death and delays motor function decline (Kong et al., 2014). Membralin, an endoplasmic reticulum (ER) membrane protein, exhibits reduced levels in the human ALS spinal cord and SOD1^{G93A} mouse models. The removal of membralin in astrocytes leads to a significant buildup of extracellular glutamate, resulting in glutamatergic toxicity in motor neurons due to decreased expression of the astrocytic glutamate transporter EAAT2/GLT-1. In contrast, the overexpression of membralin in astrocytes with SOD1^{G93A} mutation, enhances EAAT2/GLT-1 expression and improves motor neuron survival (Jiang et al., 2019). In individuals with a high loss of EAAT2/GLT-1 protein, no changes in EAAT2/GLT-1 mRNA were observed in the motor cortex of ALS patients. This suggests that the abnormality in EAAT2/GLT-1 may be related to post-translational processes (Bristol and Rothstein, 1996). EAAT2/GLT-1 is downregulated in rats expressing a mutant version of human TDP-43 in astrocytes, resulting in motor neuron death (Tong et al., 2013). In conclusion, EAAT2/GLT-1 downregulation, a consistent finding in both ALS patients and animal models, plays a pivotal role in ALS pathogenesis. This downregulation leads to glutamate accumulation, causing excitotoxicity and motor neuron degeneration.

**D-Serine**

D-serine acts as a co-agonist at the NMDAR's glycine site. Increased level of this amino acid could theoretically cause excitotoxicity. D-serine levels in ALS patients' plasma were substantially greater than in healthy control subjects (Lee et al., 2021). D-serine levels in the spinal cord have been found to be higher in both sporadic patients of ALS and SOD1^{G93A} mice model of ALS (Sasabe et al., 2007). D-amino acid oxidase (DAO) is an enzyme responsible for the degradation of D-serine, and a mutation in codon 199 of DAO has recently been found to cause ALS phenotype (Kondori et al., 2018). This evidence among others has regained attention to the importance of NMDAR in ALS (Spalloni et al., 2013). As NMDAR has been so far neglected due to the presence of evidence for irrelevance of NMDAR activation and motor neuron death in ALS mice (Ikonomidou et al., 1996), Recent studies have shown promising results for memantine, which is a NMDAR antagonist used in the treatment of ALS models and patients (Wang and Zhang, 2005; de
Therefore, it is important to reconsider the role of NMDAR in ALS, and hopefully, the ongoing trials will elucidate the efficacy of NMDAR antagonists as a treatment for ALS (Wong et al., 2022).

Cysteine/glutamate antiporter system

Through carrying cysteine into the cell for glutathione production and releasing glutamate into extrasynaptic space, the cysteine/glutamate antiporter system (system \( X_{c^-} \)) contributes to oxidative stress and excitotoxicity. It is made up of two subunits: SLC3A2, which is found in many amino acid transporters, and xCT/Slc7a11, a 12 transmembrane domain protein that forms the channel (Gasol et al., 2004). The xCT deletion significantly reduced the progression of the disease in ALS mice, resulting in increased motor neuron survival (Mesci et al., 2015). The oxidative environment present in the SOD1G93A transgenic mice's spinal cord may upregulate system \( X_{c^-} \), resulting in an increase in glutamate release (Liu et al., 1998). Presymptomatic 70-day-old transgenic mice with the SOD1 G93A mutation showed an increase in cysteine uptake, while EAAT function showed no change. These findings suggest that the early increase in glutamate levels may be attributed to heightened system \( X_{c^-} \) activity rather than reduced EAAT activity (Albano et al., 2013). A study tried to elucidate the mechanism that links microglia to ALS progression. The study revealed that xCT was predominantly present in microglia. In addition, activated microglia were found to release glutamate primarily through the system \( X_{c^-} \) (Mesci et al., 2015). However, a recent study found that xCT is predominantly expressed in astrocytes in the spinal cord of sporadic ALS patients (Kazama et al., 2020). This discrepancy might be due to species differences (i.e., human vs. mice). In general, sporadic ALS is not linked to a mutation in SOD1, and clinical findings in sporadic ALS patients differ significantly from those in SOD1G93A mutant transgenic mice in many ways (Wijesekera and Leigh, 2009). It's evident from these discrepancies that system \( X_{c^-} \) requires further investigation to pinpoint the location of its expression, assess its role in elevating glutamate levels in the synaptic region, and determine its involvement in inducing excitotoxicity in ALS.

Excitotoxicity and Epilepsy

Epilepsy is a central nervous system disease marked by recurrent loss of consciousness accompanied with or without seizures and abnormal electrical activity in the brain. It is defined as the clinical manifestation of aberrant and excessive neuronal discharge in the brain (Mayuri, 2019). Epilepsy is the third greatest cause of global disease burden for neurological illnesses, affecting 65 million people worldwide (Devinsky et al., 2018). Initial injuries that can lead to seizures include head trauma, childhood seizures, hypoxia, or status epilepticus (SE), which is characterized by either a single seizure lasting longer than 5 minutes or a series of seizures occurring closely together with no recovery of consciousness between them (Knake et al., 2009). The intense seizure activity observed in SE results in the excessive release of glutamate, leading to overstimulation of glutamate receptors and subsequent massive influxes of calcium ions, ultimately triggering widespread neuronal death through glutamate excitotoxicity mechanisms (Walker, 2018). Following the initial injury, there is a latent period that may extend up to several years during which complex molecular, biochemical, and structural changes take place. These changes encompass alterations in synaptic plasticity, reorganization of neuronal connectivity, and the restructuring of neuronal networks (Green et al., 2021). The resulting transformation in neural circuitry can underlie the process of epileptogenesis. In the subsequent sections, the review will delve into the disruptions that occur in the regulatory mechanisms responsible for maintaining glutamate homeostasis, which may occur during the epileptogenesis process.

Vesicular glutamate transporter

Vesicular glutamate transporter (VGLUT) is responsible for glutamate loading in synaptic vesicles. In patients with temporal lobe epilepsy (TLE) accompanied by hippocampal
sclerosis, VGLUT1 exhibits a downregulation in regions characterized by neuron loss while showing elevated expression in the dentate gyrus. This pattern suggested the potential development of new glutamatergic synapses through mossy fiber sprouting. In contrast, in patients without hippocampal sclerosis, VGLUT1 exhibits an upregulation, which may contribute to hyperexcitability by increasing glutamatergic transmission (Kim et al., 2005; Hel et al., 2009). A more recent study found no difference in hippocampus VGLUT1 mRNA and protein levels between TLE tissue with hippocampal sclerosis and normal tissue, but VGLUT2 protein was downregulated and VGLUT3 protein was considerably increased (Liefferinge et al., 2015).

**Glutamate release machinery**

Calcium entry in presynaptic neurons is controlled by voltage-gated calcium channels during the neurotransmitter release process. Calcium channels have been linked to epilepsy, and genetic mutations in them have been observed in both human and rodent epilepsy models (Rajakulendran and Hanna, 2016). Cav3.2 calcium channel exhibits increased expression in the pilocarpine model of epilepsy, and its genetic deletion protects against SE-induced neuropathological hippocampus damage and ameliorates chronic epilepsy development (Becker et al., 2008). The synaptic machinery is altered in the amygdalar kindling model when the 7S soluble N-ethylmaleimide sensitive factor (NSF) attachment protein receptor (7S SNARE) complex, which is involved in synaptic vesicle release, accumulates in hippocampal synapses for up to a year after the kindling stimuli are stopped (Matveeva et al., 2012). Syntaxin 1B is a key component of the SNARE complex, and its mutation has been linked to epilepsy (Vardar et al., 2020).

In a process known as gliotransmission, astrocytes can also release glutamate. It was postulated that astrocytes in sclerotic hippocampal tissue could have activated molecular pathways that promote glutamate transmission, and that this glutamate release might provoke seizure activity (Lee et al., 2007). In a pilocarpine model of epilepsy, genetic deletion of the SNARE domain in astrocytes reduced seizure frequency and delayed seizure onset (Clasadonte et al., 2013). In the epileptic hippocampus of a chronic model of TLE rats, it was shown that increased calcium-dependent glutamate release from hyperexcitable astrocytes up-regulates excitatory neurotransmission (Álvarez-Ferradas et al., 2015). Tumor necrosis factor-alpha (TNFα) is responsible for the abnormal glutamate release from astrocytes. This occurs via an autocrine mechanism involving astrocyte-derived ATP/ADP activating P2Y1 receptors. Notably, blocking P2Y1 receptors has been found to restore normal excitatory synaptic activity in the inflamed hippocampus (Nikolic et al., 2018).

**Ionotropic and metabotropic receptors**

AMPA play an important role in the initiation of seizures, with AMPAR inhibition proving more effective than NMDAR inhibition (Hanada, 2020). In the hippocampus of TLE rats with fast ripple activity, there is an increase in immunoreactivity of glutamate receptors, including NMDAR and AMPAR (Chiprés-Tinajero et al., 2021). Epilepsy has also been linked to mGluRs, which are divided into three groups. Group I includes mGluR1/5, primarily found postsynaptically, and modulates neuronal excitability by influencing ionotrophic glutamate receptor activation. Group II comprises mGluR2/3, predominantly located in presynaptic terminals, and inhibits presynaptic glutamate release. Group III encompasses mGluR4, 6, 7, and 8, serving as inhibitory presynaptic receptors (Barker-Haliski and White, 2015). Elevated mGluR1 mRNA levels have been observed in the hippocampus of animal models of epilepsy and dissected human tissue, indicating a contribution to hippocampal hyperexcitability (Akbar et al., 1996; Blümcke et al., 2000). Activation of group I mGluRs during glutamate exposure triggers proteolysis of the fragile X mental retardation protein (FMRP), a translation repressor, leading to increased protein synthesis and facilitation of group I mGluR-mediated epileptogenesis (Zhao et al., 2015). mGluR antagonists hold promise for the development of antiepileptogenic medications (Tang et al., 2009). For instance, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), a group 1 mGluR antagonist, has demonstrated the reduction of SE, neuronal loss, and epileptogenesis (Tang et al., 2007). In the chronic
stage of kainic acid-induced SE in rat (stage of occurrence of spontaneous and recurrent seizures), downregulation of mGluR2/3 was observed in the stratum lacunosum moleculare. Reduced mGluR2/3 receptor density was noted in the temporal cortex during the latent period, while a significant reduction in density occurred in the CA1 and temporal cortex during the acute stage (a stage follows kainic acid injection that built up progressively into a status epilepticus and lasts for few hours), potentially indicating a decreased inhibitory effect contributing to hyperexcitability (Ali et al., 2016). In a recent study, a rat epilepsy model during the latent phase has shown higher mGluR5 mRNA levels in the dorsal and ventral hippocampus, alongside lower expression of group III genes in the hippocampus and temporal cortex, potentially contributing to epileptogenesis. While most changes in expression during the latent phase were not observed in the chronic phase, mGluR8 mRNA levels remained low in the hippocampus. Furthermore, alterations in the gene expression of group II mGluRs were predominantly seen in the chronic phase, marked by increased mGluR2 in the dorsal hippocampus and temporal cortex (Kovalenko et al., 2022). mGluRs are found on astrocytes as well. When compared to controls, astrocytic mGluR1 and mGluR5 are elevated in the hippocampi of epilepsy patients with hippocampal sclerosis. This elevation may contribute to epileptogenesis through the activation of specific signaling pathways (Aoki et al., 2019). The upregulation of group I mGluR, and the downregulation of group II and III mGluR in different brain regions potentially play a significant role in the pathophysiology of epileptogenesis. This intricate balance of mGluR subtypes highlights their potential involvement in the development and progression of epilepsy, warranting further investigation into their roles and therapeutic implications.

**Excitatory amino acid transporter**

EAAT expressed on astrocytes has been implicated in epilepsy. In individuals with TLE who developed hippocampal sclerosis, there was a reduction in astrocytic EAAT2/GLT-1 expression. (Proper et al., 2002). In epileptic hippocampi of individuals with intractable treatment-resistant TLE, both EAAT1/GLAST and EAAT2/GLT-1 levels were found to be lower (Sarac et al., 2009). Increased EAAT2/GLT-1 expression protects mice from SE-induced death, neurodegeneration damage, and chronic seizure onset in a pilocarpine-induced SE model (Kong et al., 2012). Ineffective glutamate reuptake can result in glutamate buildup in the extracellular space, causing hyperexcitability and the development of epilepsy.

**Discussion**

It has now been two decades since Olney first proposed the concept of excitotoxicity as a mechanism to understand the neurotoxicity of glutamate and as a potential etiological factor in neurodegenerative diseases. During this time, significant progress has been achieved in elucidating the cellular mechanisms of excitotoxicity, establishing its role in the pathogenesis of neurodegenerative diseases, and assessing the potential for anti-excitotoxic drug treatments (Lau and Tymianski, 2010). Recent years have witnessed substantial advancements in our understanding of the nature and diversity of receptors involved in glutamatergic neurotransmission. This, in turn, has led to the development of numerous pharmacological agents with varied mechanisms of action. Nevertheless, despite the considerable advances, the majority of human clinical trials in ALS have regretfully failed to demonstrate the desired clinical efficacy (Petrov et al., 2017). Similarly, in the context of epilepsy, available evidence indicates that the efficacy and tolerability of drug treatments have not made substantial progress, especially for patients resistant to antiepileptic drugs (Löscher and Schmidt, 2011). This implies that there is untapped potential in the synthesis of more selective ligands to address these issues.

Even though academic science has made significant progress in attempting to elucidate molecular, genetic, and environmental aspects of ALS and epilepsy. The failure to develop effective drugs may be partially attributed to the inadequacy of mouse models in representing ALS and epilepsy (Löscher and Schmidt, 2011; Petrov et al., 2017). It’s important to notice that all of the ALS rat models discussed in the review
represent familial ALS such as SOD1<sup>G93A</sup> rat model, but it’s important to take into account that only about 10% of all patients present with a familial ALS, with the remaining 90% of patients presenting with sporadic ALS. Reprogramming of sporadic ALS patients' fibroblasts into induced pluripotent stem cells and differentiation into affected neurons that show a sporadic ALS disease phenotype could provide a cellular model for disease mechanism studies and drug discovery (Burkhardt et al., 2013). In the meantime, currently available preclinical models should be considered useful only to a certain extent, with the ultimate test of the potential efficacy of any novel pharmaceutical having to come from large-scale human clinical trials (Lösch and Schmidt, 2011; Petrov et al., 2017). There is a pressing need to dedicate research efforts to develop more accurate and relevant models, as they hold the potential to provide new insights for understanding the pathophysiology of these two complex diseases and develop effective drugs.

Turning our attention to monosodium glutamate (MSG), one of the most widely used food additives in commercial foods, is needed to assess its impact on human health. This commonly used food ingredient has been found to increase the levels of free glutamate in the brain, potentially exposing individuals to risks of neurodegenerative diseases and epilepsy (Niaz et al., 2018; Ahanger et al., 2021; Singh and Panda, 2023). Despite the potential risks, people keep consuming MSG in increasing amounts, without fully realizing the possible consequences, which may have been underestimated (Niaz et al., 2018). Given this, further studies are critical to assess the toxicity of MSG and the link between MSG consumption and the development of ALS and epilepsy.

It is noteworthy that the entire story does not solely revolve around neurons and glutamate; there are other factors that warrant our attention. Glial cells, which were long overlooked and considered merely as support cells, have now been shown to play an essential role in regulating brain function and contributing significantly to neurological diseases. Research has revealed that glial cells express a diverse array of membrane proteins and channels. There is a growing body of evidence indicating that glial cells can monitor synaptic activity, regulate glutamate levels in the synapse, and release signaling molecules capable of altering neuronal activity. Disruptions in their functioning can contribute to conditions such as ALS and epilepsy (Lasiene and Yamanaka, 2011; Heuser et al., 2014). Furthermore, while this review primarily focuses on glutamate, other excitatory amino acids, such as aspartate, which acts as an NMDA receptor agonist, have also been implicated in ALS and epilepsy (Flavin and Seyfried, 1994; Lewerenz and Maher, 2015). Additionally, it is worth exploring the role of other glutamate receptor co-agonists, like D-serine, in excitotoxicity, especially in the context of ALS and epilepsy. A more in-depth investigation into these substances and their interactions may offer valuable insights (Sasabe et al., 2007; Ma et al., 2019).

**Conclusion**

Hyperexcitability is a common feature between ALS and epilepsy. Glutamate could be an important mediator of such hyperexcitability, so this has pushed research to investigate extensively glutamate regulation mechanisms. Regulation of glutamate in the brain and its co-activators such as D-serine is critical because abnormal glutamate levels or impaired glutamate receptors activity may induce the development of diseases. Disruption in glutamate levels in the brain can happen through different mechanisms including improper glutamate release from presynaptic nerve terminal or impaired glutamate reuptake/release by associated glial cells. Regulation of glutamate function is also controlled through glutamate receptors. Disruption in glutamate receptors distribution or defective subunits can contribute to the toxic effect of glutamate. The expanding knowledge on glutamate function and its dyshomeostasis during neurological disorders pave the way to developing therapeutic agents that can treat several neurological diseases.

**Acknowledgments**

I would like to thank Professor Nasr Radwan for his continuous support and guidance on this project.
Corresponding Author

Hisham Ahmed
Cairo University
Yehia Tawfiq St.
vet19101008@stud.vet.cu.edu.eg

References


Chiprés-Tinajero GA, Núñez-Ochoa MA, Medina-Ceja L (2021) Increased immunoreactivity of glutamate receptors, neuronal nuclear protein and glial fibrillary acidic protein in the hippocampus of epileptic


Serine is a key determinant of glutamate toxicity in amyotrophic lateral sclerosis. EMBO J 26:4149–4159.


Takuma H, Kwak S, Yoshizawa T, Kanazawa I (1999) Reduction of GluR2 RNA Editing, A Molecular Change that Increases Calcium Influx through AMPA Receptors, Selective in the Spinal Ventral Gray of Patients with Amyotrophic Lateral Sclerosis.


