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Implications of Glutamate Transporter-1 in Neurodegeneration-AssociatedCognitive Impairments

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Abstract

Glutamate Transporters-1 (GLT-1), also recognised as Excitatory Amino Acid Transporter 2 (EAAT2)are essential for managing glutamate levels in the central nervous system. In the brain, GLT-1 is mainly responsible for glutamate clearance from the synaptic cleft. Brain tissue can accumulate extracellular glutamate by inhibiting glutamate uptake into glial cellsdue to the inhibition of GLT-1 on neuronal glial cells. Hippocampal GLT-1 upregulations canalleviate cognitive dysfunctions in neurodegenerative conditions like amyotrophic lateral sclerosis, Parkinson's, Alzheimer's disease, *etc*.The aetiology of GLT-1 impairment in these conditions encompasses oxidative stress, inflammation, and genetic alterations. Oxidative stress can potentially harm GLT-1 by diminishing its ability to efficiently uptake glutamate. Neuroinflammatory pathways may decrease GLT-1 expression and operation, exacerbating excitotoxic injury. Genetic mutations that impact the regulation of GLT-1 can hinder its function, resulting in heightened extracellular glutamate concentrations and consequent neurotoxic effects. Due to the critical role of GLT-1 in preventing excitotoxicity, researchers are investigating various therapeutic methods to boost its effectiveness. By utilizing pharmacological compounds enhancing GLT-1, there is a possibility of lowering glutamate levels and providing protection against excitotoxicity, ultimately slowing down the neurodegenerationprocess. Ongoing research aims to explore the regulatory processes involved in the expression and operation of GLT-1 to create specific treatments and detect early biomarkers for disease progression. This study describes the regulatory mechanism of neuronal glutamate production and its potential therapeutic application in treating neurodegenerative conditions.

Keywords: Glutamate Transporters, Alzheimer's disease, Glutamate excitotoxicity, Neuro inflammation, Oxidative stress

1. INTRODUCTION

Glutamate serves as the primary excitatory neurotransmitter within the central nervous system, being among the most prevalent anions derived from glutamic acid (Martami and Holton, 2023). Glutamate functions as the principal excitatory neurotransmitter in the central nervous system, representing one of the most abundant anions originating from glutamic acid. (Vandenberg and Ryan, 2013). Glutamate's role in learning and memory is crucial. By interacting with four different receptors, glutamate has increased opportunities to effectively and rapidly transmit messages between nerve cells (neurons) in the brain. This is accomplished by binding to glutamate receptors on neurons, which can activate various functions in the brain, including cognitive, motor, and sensory functions (Crupi et al.,2019).Glutamate is utilized by all primary excitatory functions in the vertebrate's brain, constituting over 90% of all excitatory functions in the human brain. Additionally, glutamate is one of the three amino acids necessary for the production of glutathione, a major antioxidant. The glutamate receptor is categorized as either ionotropic (including the NDMA receptor, Kainatic receptor, and AMPA receptor) or metabotropic (such as mGluR1 and mGluR5) (Traynelis et al., 2010). Both ionotropic and metabotropic receptors are essential for regulating synaptic plasticity. (Reiner and Levitz, 2018).

2. Brain Glutamate excitotoxicity

Glutamate excitotoxicity is a theory proposing that neuronal harm results from the overabundant discharge of glutamate and subsequent degeneration. As the principal excitatory neurotransmitter in the mammalian central nervous system, glutamate can induce heightened activation of glutamate receptors.Excitotoxicity is a common occurrence in numerous chronic disorders of the Central Nervous System, potentially contributing to conditions such as cancer, spinal cord injury, ischemic stroke, traumatic brain injury, hearing loss, and various neurodegenerative diseases of the CNS including multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, alcoholism, alcohol withdrawal, hyperammonaemia, and Huntington's disease. It is considered the primary mechanism responsible for neuronal dysfunction and cell death in acute CNS diseases. (Neves et al., 2023).

3. Glutamate transporter-1 (GLT-1)

GLT-1, also known as glutamate transporter-1, is a type of sodium-dependent protein that is often referred to as a 'high-affinity glutamate transporter'. Its primary function lies in maintaining glutamate homeostasis within the central nervous system (CNS) by eliminating surplus glutamate. (Magi et al., 2019). The primary glutamate transporter found in the brain plays a crucial role in clearing glutamate from the synaptic cleft, as well as in certain pathological situations where it releases glutamate into the extracellular space. (Liu et al., 2011). Glutamate, the primary excitatory neurotransmitter in the central nervous system (CNS) of vertebrates, can cause overstimulation of neurons and subsequent excitotoxic cell death when present at high extracellular levels. (Suarez-Pozos, et al., 2020). The astrocytic transporters GLAST and GLT-1, along with their human counterparts EAAT1 and EAAT2, play a crucial role in regulating the levels of synaptic glutamate to prevent excitotoxicity within the central nervous system. (C. Todd and E. Hardingham,2020). Glutamate is the most prevalent neurotransmitter in the brain, with concentrations reaching approximately 10 mmol/kg. The brain tissue exhibits an impressive capacity to gather extracellular glutamate by impeding its uptake into glial cells, possibly through the inhibition of GLT-1 on neuronal-glial cells (Danbolt, 2001). Glutamate excitotoxicity in Huntington's disease leads to striatal neurodegeneration and has been associated with impaired motor and cognitive functions. (Bhatnagar et al., 2023). Cerebral ischemia results in neuronal injury due to the disruption of GLT-1. (Hsu et al., 2022). Enhanced expression of GLT-1 in the hippocampus has ameliorated cognitive impairments in an animal model of epilepsy. (Ramandi et al., 2021). Manganese

has been found to induce neuronal damage through the elevation of neuronal excitotoxicity, potentially as a result of impaired glutamate transporter function. (Qi et al., 2020). The reduction of GLT-1 has been documented to increase oxidative damage in the brain. (Yan et al., 2020). GLT-1 additionally controls the production of TNF-α and NF-kB, potentially associated with inflammatory responses and the programmed cell death of neurons. (Lim et al., 2021).

4. Involvement of Glutamate transporters in neurological disorders

Glutamate is crucial as the primary excitatory neurotransmitter in the central nervous system of vertebrates, necessitating strict control over its concentrations in the brain. This has been linked to a range of neurological conditions such as amyotrophic lateral sclerosis (ALS), multiple sclerosis, Alzheimer's disease (AD), Parkinson's disease (PD), bipolar disorder, neuro HIV, manganism, ischemia, schizophrenia, glioma, (tumour-associated) epilepsy, and Huntington's disease (Pajarillo et al., 2019).

a. Alzheimer's Disease (AD)

AD is a multifaceted neurodegenerative condition distinguished by both functional and structural alterations in the brain, which are becoming more effectively observed due to advancements in modern brain imaging methods (Yildirim and Buyukiscan, 2019). Alzheimer's disease is the leading cause of dementia, responsible for 60-70% of all cases. The progression of this chronic neurodegenerative condition is characterized by a decline in cognitive function, starting with mild forgetfulness and advancing to more pronounced impairments in language, orientation, behaviour, memory, and eventually, bodily functions, culminating in death (Wang and Reddy, 2018). Excitatory neurotransmission in the central nervous system is mainly facilitated by glutamate, and its receptors play a crucial role in synaptic plasticity. The pathogenic mechanism of Alzheimer's disease is distinguished by the presence of extracellular plaques containing β-amyloid (Aβ) and neurofibrillary tangles containing tau (Majlath et al., 2014). GLT-1 plays a crucial role in transporting glutamate in Alzheimer's disease, establishing a connection between the presence of amyloid beta deposits and increased neuronal activity. (Perrin et al., 2023). Disrupted glutamate homeostasis in Alzheimer's disease (AD) leads to excitotoxicity and subsequent neuronal death. (Salcedo et al., 2023). The amyloid beta deposition could be attributed to increased glutamate excitotoxicity resulting from dysfunctional glutamate transporter 1 (GLT1) in neurons (Li et al., 2024). The amyloid cascade hypothesis posits that Alzheimer's Disease (AD) initiates in the brain through the accumulation and aggregation of beta-amyloid (Aβ) peptides in the brain parenchyma, leading to the formation of β-amyloid fibrils (Aβ42). Despite efforts to reduce the production of Aβ peptides and amyloid formation in the brain through drug interventions, there was no significant evidence of cognitive decline deceleration or enhancement in daily life activities among AD patients (Kurkinen et al.,2023).

b. Parkinson's disease (PD)

PD is a degenerative neurological condition that progresses over time and is primarily identified by symptoms such as slow movement (bradykinesia), tremors at rest, muscle stiffness (rigidity), and difficulty maintaining balance (postural instability). These symptoms collectively form what is known as Parkinsonian syndrome, making it a prevalent neurological disorder (Rewar,2015). Parkinson's disease is defined by a wide range of motor and non-motor symptoms. Patients with Parkinson's disease typically exhibit symptoms such as resting tremors, muscle rigidity, difficulty initiating movement, slow movement, and a hunched posture. Additionally, Parkinson's disease can be linked to neurobehavioral conditions like depression and anxiety, cognitive issues such as dementia, and autonomic problems like orthostatic hypotension and excessive sweating (Beitz, 2014). The clinical presentation of Parkinson's disease is currently acknowledged to be highly diverse, encompassing non-motor symptoms of significant clinical importance (Kalia and Lang,

2015). Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra of the midbrain and the formation of neuronal Lewy Bodies, which are the neuropathological features of the condition (Beitz, 2014). The altered neurotransmission in Parkinson's disease is associated with excitability, neurotransmitter release, and synaptic plasticity (Zhang et al., 2019). Glutamate-induced excitotoxicity is commonly identified as a prominent characteristic in various neurodegenerative conditions, such as Parkinson's disease (PD), and has been correlated with a diminished capability of glial cells to reabsorb and manage glutamate (Lovino et al., 2020). The pathogenesis of Parkinson's disease is linked to excitotoxicity caused by glutamate, which is associated with impaired expression of glutamate transporters. Glutamate transporter-1 (GLT-1) plays a crucial role in removing excess glutamate at synapses, particularly at dopamine synapses (Zhang et al., 2020). In a model of Parkinson's disease induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine/probenecid (MPTP/p), mice with astrocyte-specific JWA knockout (JWA CKO) showed exacerbated loss of dopamine (DA) neurons and displayed impaired motor function. Furthermore, the levels of DA and its metabolites were decreased in these mice (Wang et al., 2018). The buildup of glutamate at the synapse within normal levels can be harmful, leading to apoptotic cell death caused by an excessive influx of Ca2+ when glutamate receptors are overstimulated. Excitotoxicity induced by glutamate is recognized as a prevalent feature in numerous neurodegenerative diseases, such as Parkinson's disease, and is associated with changes in the levels of glutamate transporters and receptors, potentially connected to inflammatory mechanisms (Iovino et al., 2020).

c. Huntington’s disease (HD)

HD is a neurodegenerative disorder inherited in an autosomal dominant manner, known for its neuropsychiatric symptoms, movement disorder (typically choreiform), and gradual cognitive decline. The condition is linked to a CAG expansion within the HD gene. Initial signs typically manifest during middle age, presenting as motor issues, cognitive deficiencies, and psychiatric manifestations that worsen as time passes(Stoker et al., 2022). Excitotoxicity has been suggested as a key contributor to the vulnerability of striatal neurons in Huntington's disease (HD). Impaired glutamate uptake by glial cells could result in excessive activation of glutamate receptors at the synaptic level in individuals with HD as well as in animal models of the disease (Huang et al., 2010). The regulation of glutamate levels within the synaptic cleft is carefully managed through the dynamic interaction of glutamate release and glutamate clearance mechanisms (Kim et al., 2011). Huntington's disease (HD) is associated with reduced expression of glutamate transporter 1 (GLT-1) in the striatum, as evidenced in post-mortem tissue and animal models. Notably, ceftriaxone has been shown to elevate GLT-1 levels in the striatum and improve motor impairments in the aggressive R6/2 mouse model of HD (Wilkie et al.,2020). Various pathological mechanisms such as N-Methyl-D-Aspartate (NMDA) receptor-mediated excitotoxicity, dopaminergic dysfunction, mitochondrial dysfunction, oxidative stress, dysregulated autophagy, aberrant protein aggregation, disrupted gene transcription, and trophic support loss contribute to the development of Huntington's disease. These abnormalities are thought to be partially associated with an increase in the toxic function of mutant huntingtin (mHTT) and a decrease in normal HTT function. Glutamate-mediated excitotoxicity has been implicated in HD, as elevated levels of glutamate have been identified in the cortex of deceased individuals with HD. This phenomenon may be attributed to impaired astrocyte function, as diminished expression of astrocytic glutamate transporter (EAAT1) and GLT-1 mRNA has been observed in the neostriatum of post-mortem human HD brains. (Kim et al., 2021). HD is characterized by dysfunction in glutamate neurotransmission, believed to play a key role in the manifestation of the disease. The presence of mutant HTT (mHTT) proteins has been associated with the targeted degeneration of medium spiny neurons (MSNs) through the

sensitisation of glutamate receptor-induced intracellular Ca2+ release, leading to neuronal excitotoxicity (Ibrahim et al., 2023).

d. Schizophrenia

Schizophrenia is a complex mental illness that disrupts various cognitive functions, including memory, thinking, perception, and willpower (Fumero and Gonzalez, 2013). Schizophrenia is characterized by reductions in the GABAergic neurotransmitter system across various brain regions, affecting both presynaptic and postsynaptic elements. While the hyperdopaminergic theory associated with schizophrenia psychosis could potentially be linked to reduced midbrain GABAergic inhibitory neurotransmission, there is currently no evidence of molecular changes supporting this hypothesis. It was theorized that a lower number of GABA-related molecular markers would be observed in the midbrain of individuals suffering from schizophrenia and that these markers would be linked to alterations in dopaminergic molecules. Additionally, it was hypothesized that the downregulation of markers for inhibitory neurons would be more pronounced in schizophrenia patients with heightened levels of neuroinflammation (Purves-Tyson et al., 2021). The psychotomimetic effects of NMDA receptor antagonists suggest a disruption in glutamatergic signalling. Thankfully, various preclinical and clinical investigations have pinpointed multiple promising avenues for boosting NMDA receptor activity and restoring balance to glutamatergic levels. These include targeting the glycine transporter GlyT1, the muscarinic acetylcholine receptors M (1) and M (4), as well as the metabotropic glutamate receptors 2, 3, and 5 (Field et al., 2011). Dysregulation of the glutamate transporters EAAT1 and EAAT2, along with their isoforms, has been associated with schizophrenia. The expression of EAAT1 and EAAT2 has been investigated in various brain regions; however, the predominance of astrocytic glutamate transporter expression encompasses the relatively minor changes in excitatory amino acid transporter (EAATs) isoforms in neurons in the cortex. The dysfunction of the glutamatergic N-methyl-D-aspartate (NMDA) receptor plays a crucial role. Investigations into medications that modulate the activation or inhibition of NMDA receptors have been conducted in schizophrenia and major depression, showing potential in addressing negative symptoms, cognitive impairments, and mood disturbances (Hashimoto et al., 2013). Repeated administration of phencyclidine (PCP) in mice's prefrontal cortex (PFC) induces a range of schizophrenia-like psychobehavioral abnormalities and reduces extracellular glutamate levels, a phenomenon associated with elevated levels of glial glutamate and aspartate transporter (GLAST) (Uchida et al., 2019).

e. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal central nervous system neurodegenerative disease of unknown cause. Commonly referred to as motor neuron disease, it is distinguished by the progressive degeneration of upper and lower motor neurons in the spinal cord and brain, resulting in muscle weakness and eventual paralysis. While ALS has historically been categorized as a neuromuscular disorder, recent imaging and neuropathological findings suggest the potential involvement of non-motor neurons in the pathogenesis of the disease (Hardiman et al., 2017). The precise mechanisms leading to the specific demise of motor neurons in ALS are not completely elucidated, however, an expanding body of evidence points towards the involvement of glutamate-mediated excitotoxicity in the degenerative processes of motor neurons in ALS. Animal models of ALS and ALS patients have shown decreases in the glutamate transporter GLT1 in the motor cortex and spinal cord. Nonetheless, it is still uncertain whether the reduction in GLT1 is the primary factor responsible for the degeneration of motor neurons in ALS (Sugiyama and Tanaka, 2018). Amyotrophic lateral sclerosis (ALS) induces excitotoxicity through heightened glutamate secretion, alterations in postsynaptic glutamate receptors, and reduced functionality of astrocytic glutamate transporters (Rosenblum and Trotti, 2017). Excitotoxicity is associated with acute and

chronic neurodegenerative diseases such as ischemia, Huntington's disease, and ALS, and it results from excessive stimulation of glutamate receptors (Foran and Trotti, 2009). Glutamate-induced excitotoxicity has been identified as a crucial factor in the pathogenesis of motor neuron diseases such as amyotrophic lateral sclerosis (ALS).

f. Neuro HIV

The primary stage of human immunodeficiency virus type 1 (HIV-1) infection is characterized by the period immediately after contracting HIV until seroconversion is achieved (Brew and Garber, 2018). HIV-1 and its proteins are responsible for causing glutamate excitotoxicity by elevating glutamate levels in areas of intense synaptic activity. This study aims to examine the influence of HIV-1 transactivator of transcription (Tat) from clade B on ephrinA3, and its role in regulating glutamate levels in co-cultures of human astrocytes and neurons. Despite the higher susceptibility of glial cells due to their abundance in the central nervous system, they serve as reservoirs for HIV rather than neurons in the brains of HIV-positive individuals. Glutamate excitotoxicity is the primary cause of neuronal death in HIV-positive individuals (Singal et al., 2021).

g.Epilepsy

Epilepsy is a chronic neurological disorder characterized by recurrent seizures due to neuronal hyperexcitability and sudden, synchronized bursts of electrical discharges. Impaired astrocyte function leading to glutamate excitotoxicity is known to be a key player in the pathogenesis of epilepsy. Excitatory amino acid transporters (EAATs) are vital in maintaining low extracellular glutamate levels in the nervous system and preventing excitotoxicity (Green et al., 2021). Excessive levels of extracellular glutamate within the brain lead to the hyperstimulation of glutamate receptors, resulting in glutamate excitotoxicity, which in turn initiates the influx of calcium ions and subsequent cell demise (Green et al., 2021). Several studies have indicated that glutamate excitotoxicity and calcium overload in neurons are responsible for neuronal death during seizures. Research has shown that elevated levels of glutamate in epileptogenic foci contribute to the initiation and propagation of seizures by increasing extracellular glutamate levels in the brain (Sarac et al., 2009, Thomas et al., 2004; Haliski and White, 2015). Furthermore, studies have indicated that the existence of cytokines and reactive oxygen species triggers astrocyte cells in the context of status epilepticus (SE). As a result of the reduced clearance of glutamate caused by this phenomenon, there is an accumulation of glutamate in the extracellular space, thereby increasing the likelihood of neuronal excitotoxicity (Sanchez et al., 2018,Matute et al.,2006). Moreover, it was illustrated that incorrect glutamate release from a sole astrocyte could induce rises in intracellular Ca2+ via NMDA receptors in numerous nearby neurons (Haliski and White, 2015, Sarac et al., 2009). The outcome could lead to a rise in the astrocytes' internal calcium levels, potentially boosting the release of glutamate and facilitating excitotoxicity (Sarac et al., 2009, Aguado et al., 2002, Rothstein et al., 1993). Studies have demonstrated that the activation of mGluRs and the excessive release of glutamate by astrocytes are causally connected to excitotoxic processes that result in a large number of populations of neurons firing simultaneously during seizures (Lin et al., 2012, Wetherington et al., 2008, Sanchez et al., 2018,Tian et al., 2005, Benarroch, 2009).

Table 1.Nomenclature of glutamate transporters, main biological activity, and predominant expression in the CNS.

Protein name (human)	Protein name (rodent)	Gene	Main biological activity	Predominant expression in mature brain	References

Protein name (human)	Protein name (rodent)	Gene	Main biological activity	Predominant expression in mature brain	References
EAAT1	GLAST	SLC1A3	Glutamate transporter	Astrocytes, olygodendrocytes in cerebellum, cortex, spinal cord (perisynaptic)	(Storck et al., 1992,Tanaka, 1993,Arriza et al., 1994)
EAAT2	GLT-1	SLC1A2	Glutamate transporter	Astrocytes (perisynaptic), axon terminals (presynaptic), oligodendrocytes in whole brain and spinal cord	(Haugeto et al., 1996,Arriza et al., 1994)
EAAT3	EAAC1	SLC1A1	Glutamate and cysteine transporter	Neurons (postsynaptic, cell soma and dendrites) in whole brain	(Arriza et al., 1994, Kanai and Hediger., 1992)
EAAT4	EAAT4	SLC1A6	Glutamate transporter, glutamate-gated chloride channel	Neurons (postsynaptic, dendritic spines) in cerebellum	(Fairman et al., 1995)
EAAT5	EAAT5	SLC1A7	Glutamate-gated chloride channel	Neurons (presynaptic) in retina	(Arriza et al., 1997)
vGLUT1, 2 and 3	vGLUT1, 2 and 3	SCL17A7, 6 and 8	Glutamate transporter	Mainly presynaptic throughout the brain	(Vigneault et al., 2015,Bellocchio et al., 2000, Takamori et al., 2000, Fremeau et al., 2001, Fremeau et al., 2001)
xCT	xCT	SLC7A11	Cystine-glutamate antiporter	Astrocytes, microglia retinal Muller cells, immature cortical neurons, and glioma in the CNS	(Cho and Bannai., 1990, Piani and Fontana., 1994,Bridges et al., 2012)

Conclusion

GLT-1, also known as Glutamate Transporter-1, plays a crucial role in maintaining the balance of glutamate at the synapse by removing excess glutamate. In neurodegenerative

disorders, malfunction of GLT-1 results in increased levels of extracellular glutamate, leading to excitotoxicity and neuronal death, which in turn contribute to cognitive deficits. Research indicates that decreased expression and activity of GLT-1 are linked to cognitive impairments in conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Boosting the function of GLT-1 through drugs or genetic modifications has been shown to reduce glutamate-induced excitotoxicity, safeguard neurons, and enhance cognitive abilities in animal models of these diseases. Therefore, targeting GLT-1 holds promise as a therapeutic approach for ameliorating cognitive impairments associated with neurodegeneration.

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