Review: Glutamate, excitotoxicity and related diseases

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Abstract

Glutamate is an excitatory neurotransmitter that is abundant in many central and peripheral tissues and is essential for cell survival and body homeostasis. Although its existence has been known for many years; research still reveals that excitotoxicity plays a role in the development of new pathological conditions. For this reason, glutamate and glutamate excitotoxicity must be well understood, and glutamate-related circumstances must be clarified.

Keywords: AMPAR, EAAT, Excitotoxicity, Glutamate, Kainate, mGluR, NMDAR

1. What is glutamate?

Glutamate, along with glutamine, is the most common amino acid in the human brain, and glutamate is regarded the primary excitatory neurotransmitter in the central nervous system (CNS) due to its participation in several metabolic pathways.

Glutamate was discovered in large concentrations in the brain in the 1930s; its role as a key excitatory neurotransmitter in the CNS was described in 1984.(Krebs, 1935; Perry et al., 1971). Brain tissue contains approximately 5-15 mmol / kg glutamate, the majority of which is found in neurons. Glutamate content in glutamatergic neuron cytoplasm is about 5−10 mM, several times higher than other amino acids (Ottersen, 1989; Ottersen et al., 1992).

Glutamate has a major role in normal brain functions like learning, memory, cognition. Also, during central nervous system development, it's involved in cell migration, differentiation, formation of synapses and cell death (Danbolt, 2001; Komuro & Rakic, 1993; Mayer & Westbrook, 1987). Furthermore, because GLURs exist in both peripheral neural and non-neural tissues, it plays an important role in maintaining homeostasis in a variety of peripheral organs, including the adrenal medulla, peripheral nerves, bone and bone marrow, gut, hepatocytes, heart, lungs, kidney, spleens, ovaries, vagus, and other cholinergic nerves (Gill & Pulido, 2001; Hinoi et al., 2004).

2. Plasma membrane glutamate transporters (EAATs)

Although glutamate is required for the normal functioning of many systems, excessive glutamate stimulation causes excitotoxicity and neurodegeneration in neurons. Since there is no enzyme that can degrade glutamate, its concentration and effect are largely regulated by the rate of uptake from the

extracellular fluid. It cannot pass the blood-brain barrier and must be withdrawn from the extracellular fluid on a regular basis by glutamate transporters and presynaptic terminals in neighboring glial cells to prevent excessive receptor activation. (Bak et al., 2006; Danbolt, 2001; Vandenberg & Ryan, 2013)

Extracellular glutamate requires cellular uptake, which is mediated by excitatory amino acid transporters (EAATs) found in the plasma membranes of astrocytes and neurons (Danbolt, 2001; Featherstone, 2010; Vandenberg & Ryan, 2013). EAATs are classified into five subtypes, EAAT1–5 (O'Shea, 2002). All the five types are linked to the cotransport of 3 Na^+ and 1 H^+ followed by the counter transport of 1 K^- with one substrate molecule (Danbolt, 2001; Owe et al., 2006; Zerangue & Kavanaugh, 1996).

EAAT1 is a highly expressed and important transporter in the neocortex and cerebellum, particularly in astrocytes, as well as in a variety of other tissues including the retina, inner ear and circumventricular organs. (Berger & Hediger, 2000; Furness & Lehre, 1997; K. P. Lehre & N. C. Danbolt, 1998; Rauen et al., 1996).

All regions outside of the brain, where EAAT1 is more prevalent, contain EAAT2, which serves as the forebrain's main glutamate transporter. Although it is found in presynaptic nerve terminals, it is more abundant in astrocytes.(Mennerick et al., 1998; Niciu et al., 2012). EAAT1 and EAAT2 are the major transporters responsible for maintaining optimal glutamate in synaptic cleft while EAAT2 responsible for most of the glutamate uptake(Eulenburg & Gomeza, 2010; Knut P. Lehre & Niels C. Danbolt, 1998). According to new scientific research, a number

of disorders, including ischemia, epilepsy, Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and autism, are linked to neurotoxicity, and EAAT1/EAAT2 dysregulation may be a key factor in neuropathogenesis (Barone, 2010; Blandini, 2010; Blandini et al., 1996; Bonnet, 2000; Garcia-Esparcia et al., 2018; Li et al., 1997; Lin et al., 1998; Pajarillo et al., 2019; Scott et al., 2011; Sheng et al., 2012).

EAAT3 shows a predominantly neuronal expression, particularly at the postsynaptic terminals (Rothstein et al., 1994). It is expressed throughout the brain and is involved in maintaining low glutamate concentrations. This suggests a role in synaptic plasticity (Bjørn-Yoshimoto & Underhill, 2016). Outside of the CNS, it is thought to be the major Glu and Asp transporter in a range of cell types, including skeletal muscle and the kidney. (Hediger, 1999; Li et al., 2015).

EAAT4 is a neuron-specific glutamate transporter, has only been detected in the dendrites of cerebellar Purkinje neurons (Danbolt, 2001; Kanai et al., 2013). EAAT4 and EAAT1 are two main transporters that control glutamate levels to prevent neurotoxicity in the cerebellum (Perkins et al., 2018).

EAAT5 is selectively expressed at photoreceptors, bipolar and amacrine cells (Danbolt, 2001; Kanai et al., 2013). Its Cl- conductivity is high, therefore thought to be the glutamate-activated receptor that controls the excitability of retinal neurons (Pow & Barnett, 2000; Tse et al., 2014).

3. Glutamate Receptors

Glutamate is stored in vesicles in axon terminals, and electrical stimulation acts on glutamate receptors via Ca2+ dependent exocytosis. The receptors are

classified into two types based on their function. İonotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). The majority of nervous system cells express functioning GluR. Different forms of GluRs may be found in peripheral neuronal cells, numerous cells in non-neural tissues such as endocrine, heart, kidney, lung, ovary, testicular, bone, and most types of immune cells (Ganor & Levite, 2014; Gill & Pulido, 2001; Hinoi et al., 2004).

3.1.Ionotropic Glutamate Receptors (iGluRs)

iGluRs mediate the rapid response of the CNS. Postsynaptic membranes contain all three receptors, and each receptor has different functions in the brain. Many neurological diseases have been found to be associated with these receptors.

The receptors classified as amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate (KA), and n-methyl-d-aspartate (NMDA). (Niciu et al., 2012).

3.1.1. NMDA receptors (NMDAR)

NMDA receptors is one of the most studied glutamate receptor types as it is important for both physiological and pathological processes. They play critical roles in synaptic plasticity, a learning and memory mechanism.(Li & Tsien, 2009; Liu et al., 2004; Riedel et al., 2003; Zhu & Paoletti, 2015). They are also of significance in terms of treatment because they are effective in many neurological illnesses.

Three NMDA subunit families have been discovered: NR1, NR2A-D, and NR3A-B. NR1 and NR2 subunits combine to form heterotetramers, which are NMDA receptors (Zhu & Paoletti, 2015). With glutamate binding to NR2, glycine binding to NR1 is required for NMDA receptor opening (Johnson & Ascher, 1987). It is

hypothesized to generate triple NR1 / NR2 / NR3 tetrameric complexes in NR3-expressing cells (Sasaki et al., 2002). There are specific areas on the receptor that extracellular magnesium (Mg^{2+}) ions binds and cause blockage of the ion channel. For receptor activation, it is necessary to remove the receptor blockage caused by the Mg^{2+} ion. (Zhu & Paoletti, 2015). When ligand binding activates the receptor, ion channel opens, allowing Ca^{2+} ions to enter the cell. High permeability to calcium ions is thought to be important in synaptic plasticity (G. E. Hardingham & H. Bading, 2010; Li & Tsien, 2009; Liu et al., 2004).

In addition to roles on synaptic plasticity, NMDARs also critical for supporting neuronal survival (Hardingham, 2006; Hetman & Kharebava, 2006). Ca^{2+} levels determine cell fate; while basal NMDAR activity is required for cell survival, too much signaling produces excitotoxicity, and the absence of receptor activity induces apoptosis (Hardingham, 2006; G. E. Hardingham & H. Bading, 2010; Giles E. Hardingham & Hilmar Bading, 2010; Hetman & Kharebava, 2006; Leveille et al., 2008; Parsons & Raymond, 2014; Sattler et al., 2000). There are two models that explain the determination of whether the stimulus will be neurotoxic or neuroprotective. In the first model, the result depends on the localization of the stimulated receptor. Synaptic NMDAR activation promotes cell survival, while extrasynaptic NMDAR stimulation may cause glutamate excitotoxicity and cell death (G. E. Hardingham & H. Bading, 2010; Giles E. Hardingham & Hilmar Bading, 2010; Leveille et al., 2008; Parsons & Raymond, 2014; Sattler et al., 2000; Talantova et al., 2013). In the second hypothesis, GluN2A-NMDARs, which are linked to the

activation of pro-survival pathways including CREB and PI3K, are neuroprotective, whereas GluN2B-NMDARs, which are more associated with apoptotic signals, are excitotoxic (Liu et al., 2007; Terasaki et al., 2010).

Many CNS illnesses are characterized by NMDA receptor dysfunction. Examples include acute excitotoxic disorders like ischemic brain injury and traumatic brain injury as well as chronic neurodegenerative conditions like Parkinson's, Alzheimer's, and Amyotrophic lateral sclerosis (Beal, 1992; Hsieh et al., 2006; Koutsilieri & Riederer, 2007; Meldrum, 1994; Wang & Reddy, 2017; Zhang et al., 2019). Therefore, NMDA receptor-based approaches are also used among the treatment approaches of these diseases.

3.1.2. AMPA Receptors (AMPAR)

Among the ionotropic neurotransmitter receptors, the majority of rapid excitatory synaptic transmission in the CNS is mediated by AMPA receptors.(Palmer et al., 2005; Song & Huganir, 2002). AMPARs have intracellular pools and their numbers are regulated by endocytosis, exocytosis, and endosomal sorting. The increase or decrease in synaptic strength as a result of this dynamic regulation is widely accepted as the mechanism behind memory and learning processes, known as long-term potentiation (LTP) and long-term depression (LTD) (Diering & Huganir, 2018).

AMPA receptors are tetramers composed of four subunits (GluA1-4). Each of the subunits gives different properties to the receptor and their distribution in the brain varies regionally. GluA1, GluA2, and GluA3 subunits are found throughout the CNS, whereas GluA4 expression is limited to the cerebellum, thalamus, and brain

stem. GluA2s are seen even in the embryonic stage, while other subunits appear during development (Yadav et al., 2017).

Calcium permeability of AMPARs depends on their subunit composition. GluA2-containing receptors are Ca-impermeable, while calcium-permeable AMPARs (CP-AMPA) are involved in synaptic plasticity. The unstable state provided by calcium permeability also makes the neuron susceptible to pathological conditions. Long-term expression of CP-AMPARs has been associated with neuronal pathologies such as ischemia, drug addiction and memory deficits (Gasbarri & Pompili, 2014; Yadav et al., 2017). As a result, they are pharmacological targets for memory impairments and drug addiction illnesses, in addition to other excitotoxic ailments (Chang et al., 2012; Malinow & Malenka, 2002; Mayer, 2011).

The rapid activation and opening of the AMPA receptor, as well as sodium influx through the channels, overcomes the NMDA receptor's voltage-dependent magnesium block and improves its activation (Henley & Wilkinson, 2016; Palmer et al., 2005).

3.1.3. Kainate Receptors (KAR)

Kainate receptors found in both pre- and postsynaptic neurons so they can take role in excitatory or inhibitory neurotransmission (Huettner, 2003; Lerma, 2006). Postsynaptic Kainate participate in reducing magnesium block of NMDA while presynaptic one help to modulate release of GABA (Huettner, 2003). It’s also clear that KA receptors participate in short and long-term synaptic plasticity (Bortolotto et al., 1999).

Kainate receptors are also made up of various subunits: The GluR5-7 and KA1-2 receptors (Mayer, 2011; Mayer & Armstrong, 2004).

They allow ion flow right after glutamate, do not require different cofactors to activate [31,32]. Synapses containing KA receptors quite low in number comparison to NMDA and AMPA receptors (Marmiroli & Cavaletti, 2012).

3.2. Metabotropic glutamate receptors (mGluRs)

Metabotropic glutamate receptors (mGluRs) are a type of glutamate receptor that is commonly found in the central and peripheral nervous system and has many different functions. There are 3 types of mGluRs.

Group I, which includes mGluR1 and mGluR5, has mainly postsynaptic neuronal distribution and governs excitatory postsynaptic potentials via Gq or tyrosine kinases (Heuss et al., 1999).

Group II metabotropic receptors, which include mGluR2 and mGluR3, are coupled with G0 and Gi proteins, lower intracellular cAMP via suppression of the adenylyl cyclase/protein kinase A pathway. They found both in pre- and postsynaptic neurons (Ohishi et al., 1994).

Group III metabotropic receptors include mGluR4, mGluR6, mGluR7, and mGluR8 are associated with Gi and G0 proteins. All predominantly expressed presynaptically except mGluR6 which is mainly postsynaptic and also been observed in rod cells of retina (Mercier & Lodge, 2014). They function as auto- and hetero-receptors. (Cartmell & Schoepp, 2000; Zou et al., 2017).

4. Excitotoxicity

Glutamate excess causes excessive depolarization of neurons, which leads to neuronal death. This is known as excitotoxicity. This toxic process take place not only in acute but also chronic diseases of the CNS. While various conditions like traumatic brain injury, cerebral ischemia, and status epilepticus are thought to be caused by acute

excitotoxic nerve cell death, many neurodegenerative diseases including Parkinson's disease, Alzheimer's disease, Huntington's disease, and lateral amyotrophic sclerosis are believed to be caused by chronic glutamate excitotoxicity (Beal, 1992; Choi & Rothman, 1990; Lau & Tymianski, 2010; Maragakis & Rothstein, 2001; Meldrum & Garthwaite, 1990; Meldrum, 1994).

4.1. Excitotoxicity Mechanisms

The mechanisms underlying neuronal necrosis include acute mitochondrial dysfunction and loss of cellular homeostasis, leading to massive energy deficiency similar to those in other cell types. When the neurotransmitter balance is disrupted in favor of excitatory stimuli, or in the presence of metabolic or oxidative stress despite normal glutamate levels, the cell is overstimulated, resulting in a cascade of damaging effects. Although many ion balances are disturbed, there is a consensus about that influx of Ca^{2+} is the main cause of excitotoxicity and NMDARs mainly responsible for calcium entry (Choi, 1985)

Overactivation of ionotropic glutamate receptors leads to opening of voltage dependent Ca^{2+} channels resulting in large amounts of Ca^{2+} influx. IP3 synthesis is promoted by activation of metabotropic glutamate receptors, and Ca2+ release from the ER into the cytoplasm is stimulated. Cytoplasmic calcium levels increase and are sequestered in mitochondria and the ER. (Thayer & Wang, 1995; Wang & Thayer, 1996).

In mitochondria, increased Ca^{2+} influx depolarizes mitochondrial membrane and results in mitochondrial permeability transition pore(mPTP) activation. This causes; leakage of accumulated Ca^{2+}; release of pro-apoptotic factor cytochrome c into the cytosol and triggering of

caspase-dependent apoptosis; inhibition of respiratory chain enzymes that causes decreased ATP synthesis and increased generation of ROS (Duchen, 2004; Orrenius, 2004; Peng & Jou, 2010; Rao et al., 2014; Yang et al., 2011).

ROS are free radicals that are normally produced during biochemical reactions within organelles such as mitochondria, endoplasmic reticulum and peroxisomes. But if it is overproduced, cannot be neutralized by cell and reacts with lipids, proteins, carbohydrates and nucleic acids. Binding to the DNA evokes its fragmentation and results in cell death (Farooqui & Farooqui, 2009; Han et al., 2001; Muller, 2000). Oxidative stress itself can potentially open mitochondrial permeability transition pores (Nicholls, 2004).

Under excitotoxic conditions, activation of NMDARs induces Ca^{2+} influx results in activation of neuronal nitric oxide synthase (nNOS) via Ca^{2+}/calmodulin signaling (Sattler et al., 1999). NO production is also increased as a result of oxidative stress. Once intracellular NO elevate to the toxic concentrations, can react with superoxide radicals and form peroxynitrite, a highly reactive oxidant that can induce lipid peroxidation, protein dysfunction, and DNA damage (Radi et al., 1991a, 1991b; Salgo et al., 1995).

Excitotoxicity also causes cell swelling and lysis as a result of the influx of Na^+ and Cl^- via AMPA-kainate receptors and Na-K-Cl cotransporter type 1 (NKCC1) (Beck et al., 2003).

Additionally, Ca^{2+} influx activate calpain that is a calcium dependent apoptotic protease and calcineurin, a Ca^{2+} dependent cysteine protease, mediate neuronal cell death (Wang, 2000).

4.2.Excitotoxicity Related Diseases

Due to their critical functions in excitatory neurotransmission, abnormal signaling in GluRs has been linked to a variety of pathologies. This has made GluRs important pharmacological targets for therapeutic applications (Bleich et al., 2003).

4.2.1. Diseases of the CNS

Because energy is required to sustain membrane potentials, abrupt decrease of blood flow and loss of energy during ischemia conditions leads to membrane depolarization. This depolarization stimukates glutamate release and extracellular accumulation.

Energy deprivation also suppresses EAAT activity and reduces glutamate reuptake. Elevated glutamate levels lead to excitotoxicity by activation of glutamate receptors, especially NMDAr's (Katsuta et al., 1995; Park et al., 1988).

4.2.2. Alzheimer's Disease

Alzheimer's disease (AD) is the leading cause of dementia, according to the World Health Organization. Alzheimer's, a chronic neurodegenerative disease of the CNS, leads to progressive cognitive impairment, memory impairment and behavioral disorders. The pathological hallmarks of AD are neurofibrillary tangles consisting of aggregated tau, senile plaques containing extracellular β-amyloid (Aβ), Gliosis, followed by neuronal cell death and brain atrophy in later stages.

The pathophysiology of AD is complex. There are both structural and functional abnormalities, and many pathways are involved in synaptic and cellular degeneration. However, evidence suggests that glutamate toxicity also plays a role in AD. Depositions act as initiating factor for neurodegenerative pathways.

Glutamat level elevation in synaptic cleft can cause neurodegeneration in AD. Aβ plaques induce extracellular accumulation of glutamate and consequently intracellular Ca^{2+} deposits in cells next to Aβ plaques (Kamat et al., 2016; Kuchibhotla et al., 2008). Increased Ca^{2+} concentration associated with dendritic spine loss and endocytosis of NMDA and AMPA receptors through calcineurin, a calcium-dependent protein phosphatase (Hsieh et al., 2006; Sheng et al., 2012)

Moreover, β-Amyloid can inhibit uptake mechanisms of glutamate. In astrocytes exposed to β-Amyloid, glutamate uptake is significantly reduced. It has been discovered that in AD, EAAT2 makes much less glutamate uptake and EAAT expression in cells is diminished (Fernandez-Tome et al., 2004; Li et al., 1997; Scott et al., 2011). Cognitive impairment and tau pathology are reduced after EAAT2 receptor function is restored with the β-lactam antibiotic Ceftriaxone (Zumkehr et al., 2015).

-Amyloid, on the other hand, has been demonstrated in multiple studies to increase the activity of NMDARs. NMDA receptor antagonists can be used to prevent this (Alberdi et al., 2010; Texido et al., 2011).

In the normal brain, there is a balance of synaptic and extrasynaptic NMDAR activity. According to a study, β-Amyloid induces glutamate release from astrocytes and selectively activates extrasynaptic NMDARs, which are thought to be responsible for glutamate's excitotoxic action (Talantova et al., 2013).

Tau protein has also been linked to AD-related excitotoxicity, either alone or in conjunction with β-Amyloid (Pallo et al., 2016; Small & Duff, 2008). Synergic action between Aβ and tau facilitates ROS

production by impairing mitochondrial function (Quintanilla et al., 2012; Rhein et al., 2009).

4.2.3. Parkinson's Disease

Parkinson's disease (PD) is a progressive and the second most common neurodegenerative disorder (Poewe et al., 2017). Clinical symptoms include motor disturbances such as rigidity, bradykinesia, postural instability and resting tremor; as well as broad spectrum of non-motor symptoms like cognitive impairment/dementia, mood disorders, pain, autonomic disturbances, psychosis and hallucinations.

The pathological hallmarks of PD include progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) which causes striatal dopamine deficiency; and Lewy bodies that are intracellular inclusions of α-synuclein (De Pablo-Fernandez et al., 2019; Dickson, 2018).

It is also known that, beyond the dopamine system, there are disruptions in other neurotransmitters involved in the pathophysiology of PD, especially in etiology of non-motor symptoms. Two of these are glutamate and γ-amino butyric acid (GABA) (Barone, 2010; Bonnet, 2000). Degeneration of dopaminergic neurons leads to glutamate overactivity in the basal ganglia, especially in substantia nigra pars compacta (SNc) (Blandini, 2010; Blandini et al., 1996). Glutamate impairs Ca^{2+} homeostasis, and increased intracellular Ca^{2+} activates L-type Ca^{2+} channels, resulting in ROS generation in mitochondria and cell death. This process is significant in the pathophysiology of Parkinson's disease because nigral dopaminergic neurons are vulnerable to oxidative stress (Cieri et al., 2017; Surmeier &

Schumacker, 2013; Surmeier et al., 2017).

Moreover, it has been hypothesized that, even in the normal glutamate levels, indirect excitotoxicity may be one of the mechanisms in PD pathogenesis. When intracellular energy levels reduced due to mitochondrial deficits; function of Na^+, K^+-ATPase cannot generate a resting potential that is necessary for NMDAR's Mg^{2+} block and removal of the barrier allows nigrostriatal dopaminergic neurons become vulnerable to indirect excitotoxicity and cell death in the SNc (Blandini, 2010; Novelli et al., 1988).

4.2.4. Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease characterized by degeneration of spinal, bulbar and corticospinal motor neurons. It is a late-onset, fatal neurodegenerative disease that leads to muscle loss, weakness, spasticity and ultimately death. More than 90% of cases are categorized as sporadic with an unknown origin, while 5-10% of cases are familial and associated with gene mutations. (Robberecht & Philips, 2013).

Despite several research to understand the mechanism, the etiology of ALS remains unexplained. Neuroinflammation, oxidative stress, mitochondrial dysfunction, nuclear abnormalities, and abnormal RNA metabolism are all thought to have a role, and excitotoxicity is still assumed to be a significant etiological factor in ALS. (Mathis et al., 2017).

Only the spinal subtype of ALS has shown significant increases in plasma glutamate levels, with no significant increase observed in the bulbar subtype; and females had greater glutamate levels than males (Andreadou et al., 2008; Plaitakis & Constantakakis, 1993). According to studies, motor neurons in the

spinal cord are vulnerable to high glutamate levels, particularly via AMPAR and Kainate mediated excitotoxicity (Saroff et al., 2000; Vandenberghe et al., 2000; Weiss, 2011). Furthermore, EAAT2 levels were shown to be lower in the motor cortex and spinal cord of ALS patients, resulting in increased extracellular glutamate levels. Excitatory glutamate impulses cause calcium influx and motor neuron activation, which initiates damaging biochemical processes within the cell, all of which are known to be significant pathophysiological events in sporadic and familial ALS (Lin et al., 1998; Trotti et al., 1999).

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