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Glutamate toxicity in Neurological diseases

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ABSTRACT

Glutamate is a neuro transmitter and is responsible for communication between cells. Under pathophysiological conditions its concentration is increased within the brain and results in glutamate toxicity. Increased glutamate in the brain can elicit damage and ultimately neuronal death. Glutamate toxicity is associated with various neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, stroke, amyotrophic lateral sclerosis (ALS), multiple sclerosis and head trauma. However, it should be noted here that the molecular mechanism behind the glutamate toxicity is not fully understood and is quiet complex. Reducing glutamate toxicity is considered to be the most essential strategy to combat various neurological disorders. In this review, we have summarized previous studies to understand the cellular effects associated with the glutamate toxicity

Keywords: Glutamate toxicity, Neurological disorders, Alzheimer's disease, amyotrophic lateral sclerosis Glutamate transporter-1

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INTRODUCTION

Neurodegenerative diseases are one of the most challenging public health issues and their incidence is on rise. If the current incidence rate remains same, it is estimated that there will be 50% increase in Alzheimer's disease (AD) and Multiple Sclerosis (MS) over the next20 years. Neurodegenerative diseases are generally associated with the loss of function of nerve cells and even their death (Bredesen et al., 2006)[1]. The actual cause associated with neurodegeneration is not properly known and therefore the diseases arising from such condition are without proper treatment so far. One of the common phenomenon associated with the neurodegenerative diseases is rise in glutamate levels in brain or "glutamate neurotoxicity". The increased level glutamate has been reported in number of neurodegenerative conditions like Parkinson's disease (PD), Stroke, AD, MS and Amyotrophic lateral sclerosis (ALS) (Hughes, 2009)[2] (Lin et al., 2012)[3]. Approaches that reduce glutamate toxicity are considered a major therapeutic strategy to treat neurodegenerative disorders (Gardoni and Di Luca, 2006)[5] (Kim et al., 2011)[6].

Glutamate toxicity

Within the brain, glutamate is the major excitatory neurotransmitter and virtually carries out all the communication between neurons. Glutamate remains enclosed within a vesicle in presynaptic neuron. When the vesicle reaches the axonal tip, it fuses with the presynaptic membrane and ultimately glutamate is released into the synaptic space. Glutamate interacts with the glutamate receptors present on the surface of postsynaptic neuron (figure 1). As a result, the post synaptic neuron is activated and in the same manner signal gets passed from one neuron to another.

The glutamate receptors are of two types namely ionotropic receptors and metabotropic receptors (figure 1). Ionotropic ones are associated with the ion channels, while as metabotropic ones are associated with the signaling proteins like G protein and thus activate various intracellular molecules called second messengers. Both ionotropic and metabotropic receptors have emerged as potential target to treat alcohol use disorders (Goodwani S, 2017)[32]. The ionotropic receptors are further grouped into three subtypes: NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate), and kainate. Their names are with respect to a particular chemical agonists, that does not exist in the brain normally but are similar to glutamate. NMDA receptors are responsible for allowing entry of Ca^{2+} into the cells and are blocked by magnesium ions (Mg^{2+}). AMPA and kainite receptors are primarily responsible for sodium influx.

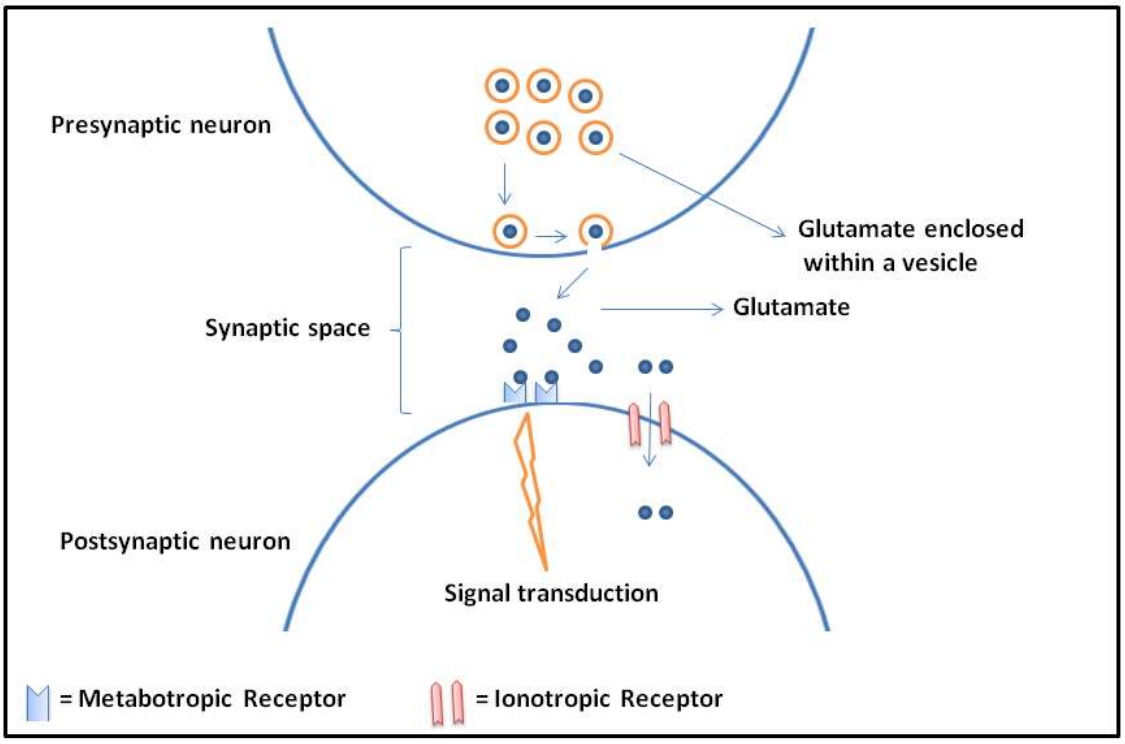

Figure 1: Transmission of signal associated with glutamate from presynaptic neuron to postsynaptic neuron.

The level of glutamate is maintained 10^{-3} M intracellularly and 10^{-5} to 10^{-6} M extracellularly in the brain (Coyle and Puttfarcken, 1993)[6] (Meldrum, 2002)[7]. However during certain pathophysiological conditions like hypoxia, ischemia and brain injury, its level is increased 50 times (Collard et al., 2002)[7]. The higher concentration of glutamate within the neurons can result in damage and ultimately neuronal death (Dore et al., 1999)[8] (Dore et al., 2000)[9]. Furthermore, activation of ionotropic glutamate receptors on postsynaptic neurons results excessive entry of Ca^{2+} inside cells and enhances reactive oxygen species (ROS) generation and ultimately neuronal death (Duchen, 2000)[33] (Henshall, 2005)[10]. The molecular mechanism associated with the glutamate-induced neuronal death is still not fully elucidated (Wang and Qin, 2010)[11]. Elevated Ca^{2+} levels inside neurons associated with glutamate toxicity results in activation of various enzymes like nitric oxide synthase, proteases, protein kinase C (PKC), phospholipases, ornithine decarboxylase, endonucleases, phosphatases and calcium/calmodulin-dependent protein kinase II. Activation of such enzymes in glutamate-induced neurons results in their damage and death. For example nitric oxide synthase produce nitric oxide (NO), which inturn initiate neurotoxic cascades and thereby results in cell death in many neurodegenerative diseases including Huntington disease (Torreilles et al., 1999)[12] (Meng et al., 2000) [13] (Zhang et al., 2000) [14]. The

elevated Ca^{2+} level in cytoplasm cleave caspases and thereby initiate apoptosis (Dutta and Trapp, 2011)[15].

Glutamate accumulation:

The accumulation of glutamate in the synaptic space is responsible for initiating neuronal death cascade. Such accumulation is attained either by releasing more and more glutamate from presynaptic neuron or by decreasing uptake by post synaptic neuron (figure 2). Normally the extracellular concentration of glutamate is about 0.6 mmol/L and when its concentration elevates to 2 to 5 mmol/L neuronal injury occurs. It should be noted here that blocking of glutamate receptors by antagonists, decline glutamate induced neuronal death. Such approach is used to treat acute ischemic events (Hirose and Chan, 1993) (Choi, 1998) (Fujisawa et al., 1993) (Popovic et al., 2000).[17-20] So far different drugs have been developed to halt glutamate toxicity and its death related processes (Gagliardi, 2000) (Adam-Vizi, 2000) (Anttila et al., 2000)[21-23].

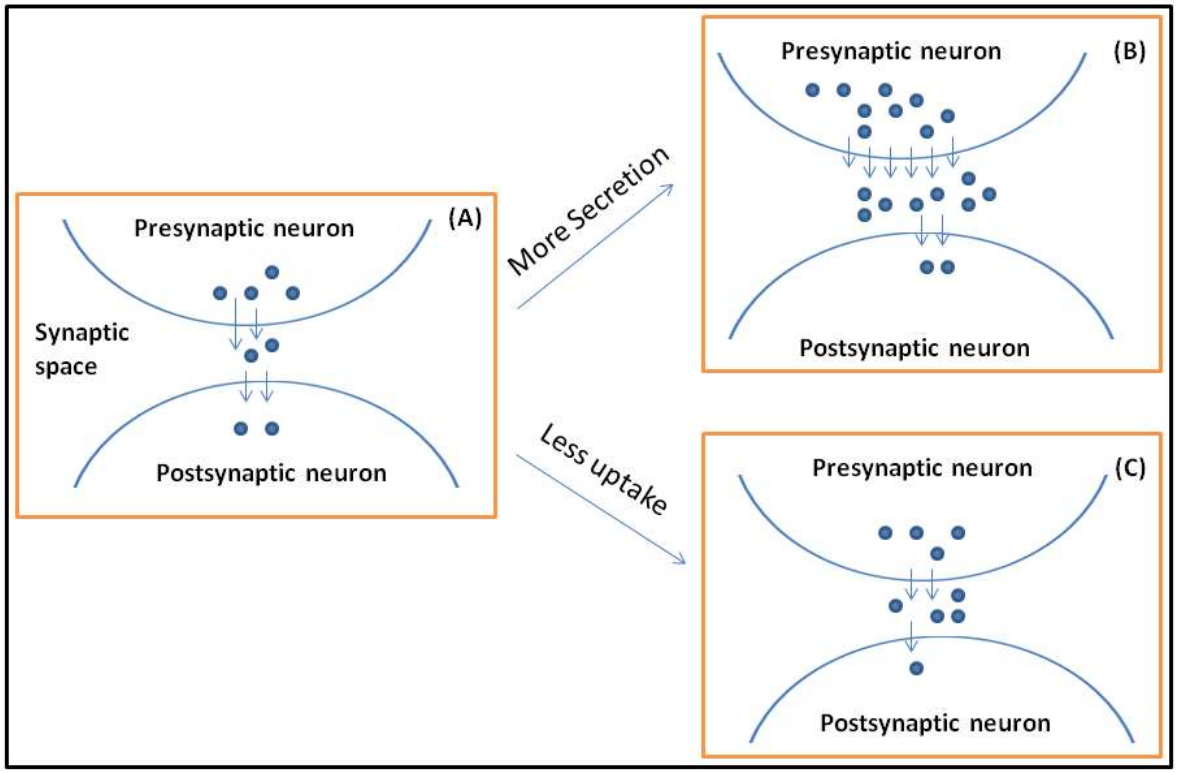

Figure 2: Shows glutamate accumulation. A) Shows normal secretion and uptake of glutamate by presynaptic and postsynaptic neurons respectively. B) Shows more secretion of glutamate into the synaptic space and therefore its accumulation. C) Shows less uptake of glutamate by postsynaptic neuron and therefore accumulation of glutamate in synaptic space.

Glutamate transporter-1 (GLT1) in neurological disorders:

As earlier stated, glutamate accumulation is highly toxic to neuronal cells and therefore its level must be tightly regulated in the brain. GLT1 is expressed mainly on astrocytes and are responsible for the clearance of glutamate from the extracellular space (figure 3). Due to its role in maintaining glutamate homeostasis, GLT1 dysregulation can have severe effects on the health of neuronal cells. It has been found that GLT1 is altered or down regulated in various neurological diseases like AD, ALS and epilepsy. Downregulation of GLT1 is considered to be the key step in the onset of spontaneous seizures during epilepsies and therefore has emerged as a promising anti-epileptic therapeutic target (Hubbard et al., 2016)[24]. Abnormality in expression of GLT1 has been observed in the ALS at post-translational level (Howland et al., 2002)[25]. In AD patients, reduced GLT1 protein level has been observed without altering mRNA level and therefore its expression is altered post-transcriptionally (Li et al., 1997)[26]. In mice, it has been found that GLT1 contributes to the pathogenesis of AD (Takahashi et al., 2015)[27]. Since GLTI is down regulated in different neurological disorders, its expression can be restored by two pharmacological approaches. The first one includes use of β-lactam antibiotic ceftriaxone, as it increases GLT1 expression via activating its promoter (Lee et al., 2008) (Rothstein et al., 2005)[28,29]. The second one include use of LDN/OSU-0212320 (a novel translational GLT1 activator) (Kong et al., 2014)[30] and has already shown a promising therapeutic efficacy in epilepsy, AD and ALS models (Kong et al., 2014) (Takahashi et al., 2015). So use of GLT1 therapeutics against different neurological disorders can only be progressed by understanding its regulation and timing precisely (Hubbard and Binder, 2017)[31].

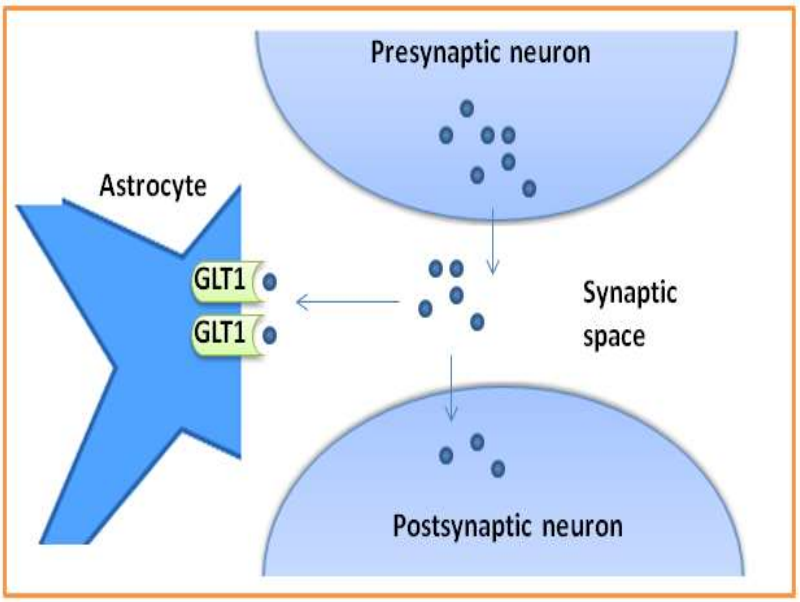

Figure 3: Shows clearance of glutamate from synaptic space by GLT1. Glutamate is released by the presynaptic neuron and it binds to receptors on the postsynaptic neuron. Glutamate is cleared from the synaptic space by GLT1. Inside the astrocyte, glutamate can be then metabolized in different ways.

CONCLUSION

Glutamate toxicity is considered to be the end common pathway that results in death of neuronal cells in many neurological disorders. Countering the glutamate toxicity produce miraculous results in prevent death and damage of neuronal cell. Although the molecular cause responsible for glutamate toxicity is still unraveled, but its understanding can wipe out many neurological disorders. It is important to focus on newer and promising strategies like combination therapies to combat glutamate toxicity induced neurodegeneration.

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