Review Article　　　　　　　　　　　　　　　　　　　　　　　　　　　　**Open Access**

Glutamate Excitotoxicity and Neurodegeneration

Ezza HSA[1]* and Khadrawyb YA[2]

[1]*Zoology Department, Faculty of Science, Cairo University, Giza, Egypt*

[2]*Medical Physiology Department, Medical Division, National Research Center, Giza, Egypt*

*Corresponding author: Ezza HSA, Zoology Department, Faculty of Science, Cairo University, Giza, Egypt, Tel: 20237753565; Fax: +202 33387758; E-mail: hebasal@yahoo.com

Abstract

Glutamate plays crucial roles in the physiology of the central nervous system as it can control many functions such as memory, learning, cognitive, emotional, endocrine and other visceral functions. In addition, glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. It has the potential to be involved in the pathogenesis of many CNS diseases either due to excessive release, reduced uptake or alteration of receptor functions. Growing evidence links glutamate excitotoxicity to various neurodegenerative diseases as cerebral ischemia, epilepsy, Alzheimer's disease, Parkinsons' disease and multiple sclerosis. In addition, several environmental pollutants result in excessive glutamatergic neurotransmission and may eventually lead to neurodegenerative diseases.

Keywords: Glutamate; Excitotoxicity; Calcium; Free radicals; Neurodegenerative diseases

Introduction

Glutamate belongs to the free amino acids that function as neurotransmitters in the Central Nervous System (CNS). These amino acids include the excitatory amino acid neurotransmitters (glutamate and aspartate) [1] and the inhibitory amino acid neurotransmitters (GABA, glycine and taurine) [2].

Glutamate is now universally recognized as being the main excitatory transmitter in the vertebrate central nervous system with up to 40% of all synapses being glutamatergic (Fairman and Amara, 1999) [3] and it is found in more than 80% of all neurons [4]. Moreover, most of the brain energy budget is required to sustain synaptic activity at glutamatergic synapses [5].

Pathophysiology of glutamate

Glutamate systems are extensively distributed throughout the brain and have been implicated in the central control of many physiological functions. As a consequence, disturbance in glutamatergic activity may underlie many psychological and neurodegenerative disorders. Excitotoxicity is triggered by the excessive release of glutamate from presynaptic nerve terminals and astrocytes into the extracellular space, with consequent over-stimulation of glutamate receptors, especially NMDA receptors [6].

The over-stimulation of both ionotropic and metabotropic glutamate receptors has clearly been implicated in the neuronal injury observed in several neurodegenerative disorders, including Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS dementia complex, and Parkinson's disease [7]. Other acute insults leading to massive brain cell death that have been related to excitatory imbalance include hypoglycemia, neurologic trauma, stroke, and epilepsy [7]. On the other hand, hypofunction of the glutamate/NMDA receptor system has been implicated in the pathophysiology of schizophrenia [8].

Role of calcium in glutamate-mediated excitotoxicity

Calcium influx was shown to be essential to glutamate excitotoxicity. Excessive stimulation of glutamate receptors can have numerous detrimental effects such as calcium homeostasis dysfunction, increased nitric oxide (NO) production, activation of proteases, an increase in cytotoxic transcription factors, and increased free radicals [9]. Generally, ion imbalance during excitotoxicity results from defects in gating ions from entering the cytoplasm as well as impairments in pumping ions out of the cytoplasm [10]. Glutamate receptor over-stimulation leads to excessive influx of Ca^{2+} (and Na^+) through glutamate receptor-gated ion channels, followed passively by movements of Cl^- and water. It causes postsynaptic neurons to be overloaded by extracellular Ca^{2+} and Na^+ as well as intracellular Ca^{2+} via release from mitochondria. The resulting combination of increased intracellular volume and Ca^{2+} overload induces various lethal metabolic derangements, internal organelle swelling, and plasma membrane failure, which leads to necrosis [11].

Molecular mechanism of excitotoxicity

Ca^+ influx initiates excitatory events involving free radical generation, mitochondrial dysfunction and activation of many enzymes, including those involved in the generation and metabolism of arachidonic acid. These enzymes include isoforms of phospholipase A2, cyclooxygenase-2 and lipoxygenases [6].

Mitochondria

Mitochondria are not only ATP producers through oxidative phosphorylation but are also regulators of intracellular Ca^{2+} homeostasis and endogenous producers of ROS. Mitochondrial injury is understood to have a critical impact on cellular energetics and excitotoxic neuronal death [12]. The mitochondria have been

implicated as a central executioner of cell death. Increased mitochondrial Ca^{2+} overload as a result of glutamate receptor over-activation has been associated with the generation of superoxide and the release of proapoptotic mitochondrial proteins, leading to DNA fragmentation/condensation and culminating in cell death by apoptosis and/or necrosis. On the other hand, it has also been well established that mitochondrial dysfunction contributes to excitotoxic death by changing membrane potential and increasing generation of ROS [12]. Excessive influx of Ca^{2+} via NMDA receptors attenuates the mitochondrial membrane potential, and leads to the opening of the permeability transition pore. Through the disruption of mitochondrial potential, excess Ca^{2+} can reduce ATP synthesis, rendering the cell more vulnerable to death insults [13]. Moreover, the release of mitochondrial cytochrome c during excitotoxicity, associated with a delayed mitochondrial depolarization and production of ROS were documented [12].

Oxidative stress is now recognized as being accountable for redox regulation involving ROS and reactive nitrogen species. Glutamate excitotoxicity is associated with higher cellular levels of ROS [12].

Peroxynitrite is a powerful oxidative molecule additionally capable of causing lipid peroxidation, direct DNA damage and protein dysfunction. Specific interactions of peroxynitrite with proteins include protein oxidation and protein nitration of tyrosine residues though protein oxidation occurs at higher rates than nitrosylation. Moreover, peroxynitrite can inhibit the normal function of cytochrome c in the electron transport chain as well as manganese and iron superoxide dismutase in scavenging superoxide via protein nitration. This interaction can potentiate caspase-mediated cell death and an eventual apoptotic cell death [14,15].

Excitotoxicity and Neurodegenerative Diseases

Glutamate excitotoxicity has been suggested to play a crucial role in almost all neurodegenerative disorders. However, the nature and symptoms differ from disease to another according to the site where neuronal degeneration takes place inside the brain (Figure 1).

Role of glutamate in cerebral ischemia

Glutamate is known to play a predominant role in the pathogenesis of ischemic brain injury. The lack of oxygen and glucose resulting from ischemia depletes cellular energy levels, which can activate glutamatergic mechanism. Glutamate and aspartate are released in the CSF of asphyxiated newborns immediately after birth and declines by 72 hours. and their initial concentrations correlated with the severity of hypoxia ischemia encephalopacy [16].

Role of glutamate in epilepsy

During an epileptic seizure, large populations of neurons in selected portions of the central nervous system abandon their normal activity and begin to fire in periodic synchronous discharges. This pathological synchronized activity is transmitted from one neuron to the next primarily through excitatory glutamatergic transmission, although GABA-ergic synapses also shape seizure-related hyperexcitability [17]. In rodent models, altering glutamate receptor or glutamate transporter expression by knockout or knockdown procedures can induce or suppress epileptic seizures. Regardless of the primary cause, synaptically released glutamate acting on ionotropic and metabotropic receptors appears to play a major role in the initiation and spread of seizure activity [18].
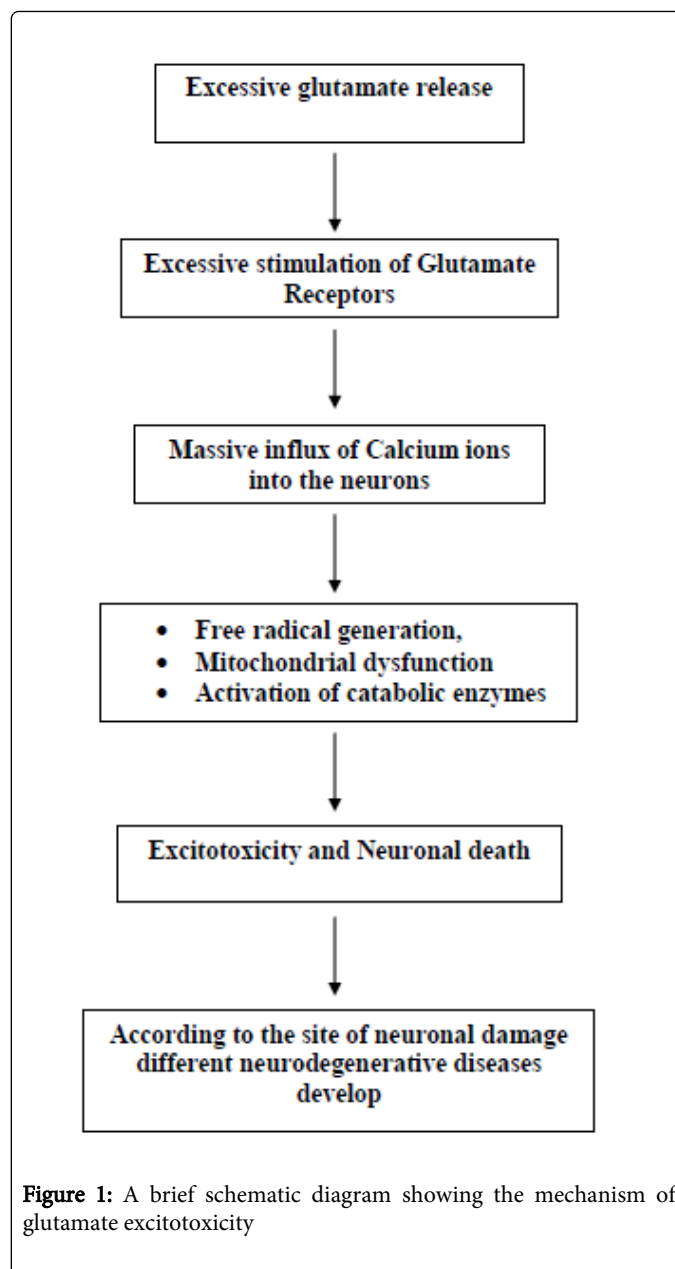

Figure 1: A brief schematic diagram showing the mechanism of glutamate excitotoxicity

Role of glutamate in Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder of the central nervous system associated with progressive cognitive and memory loss. Molecular hallmarks of the disease are extracellular deposition of the β-amyloid peptide (Aβ) in senile plaques, the appearance of intracellular neurofibrillary tangles (NFT), cholinergic deficit, extensive neuronal loss, and synaptic changes in the cerebral cortex, hippocampus and other areas of brain essential for cognitive and memory functions. According to the amyloid cascade hypothesis, AD pathogenesis is initiated by the overproduction and extracellular deposition of Aβ and the intracellular deposition of NFT. These depositions serve as initiating factors for multiple neurotoxic pathways, which may include excitotoxicity, oxidative stress, energy depletion, inflammation and apoptosis. Parameshwaran et al. [19] showed that glutamatergic signaling is compromised by Aβ-induced

modulation of synaptic glutamate receptors in specific brain regions, paralleling early cognitive deficits.

A growing body of evidence suggests that perturbations in systems employing the excitatory amino acid L-glutamate may underlie the pathogenic mechanisms of chronic neurodegeneration in AD [20].

In addition, glutamate and excessive activation of the NMDA receptor are believed to enhance the production of pathologic forms of Aβ and another Alzheimer's disease-related protein, tau. Cellular energy reduction has been associated with the elevation of the β-site amyloid precursor protein-cleaving enzyme, β-secretase, which is essential for the rate-limiting step in the formation of Aβ [21]. Thus reduction of energy levels caused by glutamate neurotoxicity may indirectly increase the production of Aβ. Hence, it seems that a vicious cycle emerges, where each pathologic condition tends to exacerbate the other. The study of El-faramawy et al. [22] showed a relationship between the increased glutamate level and the formation of tau protein in the hippocampus.

Role of glutamate in Parkinson's disease

Parkinson's disease is a neurological disorder that is caused by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the consequent massive drop of dopamine content in the striatum. These midbrain neurons project to forebrain regions, most notably the striatum, where the release of dopamine serves to regulate cortically driven firing within the basal ganglia thalamocortical motor circuits to ensure proper planning and execution of movement [23].

Glutamate is also the predominant excitatory transmitter in the basal ganglia, which is the seat of the motor deficits seen in PD [24]. In addition to sending glutamatergic projections to the striatum, the cortex also sends projections to the subthalamic nucleus (STN), thalamus, and SNpc, in addition to other nuclei in the brainstem and spinal cord. The SNpc receives further glutamatergic innervation from the STN in the indirect basal ganglia pathway. Evidence has demonstrated that the dopaminergic projection from the SNpc to various nuclei in the basal ganglia circuit exerts an important regulatory function on the firing pattern of certain glutamatergic pathways. Dopamine depletion, as seen in PD causes a complex set of changes to the functioning of the basal ganglia [23]. A sustained increase in glutamate released onto an already compromised dopaminergic cell population could elicit an excitotoxic cascade and potentiate neurodegeneration.

Role of glutamate in multiple sclerosis

Multiple sclerosis (MS) is a human neurodegenerative disorder of unknown etiology. There is growing evidence that the excitatory amino acid glutamate has an important role in the pathogenesis of MS [25]. Glutamate concentrations are increased in cerebrospinal fluid from MS patients and the levels correlate with the severity of disease [26]. Alterations in the metabolism and transport of glutamate have been identified in MS patients and changes to the balance of glutamate in CNS have been associated with local tissue damage [27]. Related work in the animal model of MS, experimental autoimmune encephalomyelitis (EAE), strongly implicates glutamate in disease development [28]. Glutamate-induced excitotoxicity is thought to contribute to oligodendrocyte and axonal loss in MS and EAE and the amino acid also exerts toxic effects on neurons [29].

Glutamate excitotoxicity and environmental pollution

In addition to the implication of glutamate in the pathogenesis of neuronal disorders, glutamate has been found to mediate the hazardous effects of some environmental pollutants. Many studies reported elevated glutamate levels in different brain areas due to exposure to different environmental pollutants which included electromagnetic radiation [30], aluminium [31], cyanide [32] and even food sweeteners as aspartame [33] and preservatives as monosodium glutamate [34]. This may result from the increase in calcium influx which leads to the release of glutamate from presynaptic terminals. Excessive glutamate may result in chronic depolarization of the postsynaptic neuron [35,36] which, in turn, may lead to increased amounts of intracellular Ca^{2+} and the activation of calcium-dependent catabolic cellular enzymes [36]. This excessive activation can result in the excitotoxic necrosis of neurons [37]. Thus potentiating or leading to the development of excitotoxicity and neurodegeneration.

Conclusion and Recommendations

Glutamate excitotoxicity has the potential to be involved in the pathogenesis of many CNS diseases either due to excessive release, reduced uptake or alteration of receptor functions. Although several studies used glutamate receptor antagonists to overcome the state of excitotoxicity, the results were unsatisfactory due to the untoward side effects or little clinical benefits. However, little attention has been given to the importance of the glutamate transporters to alleviate the excitotoxicity of glutamate. The use glutamate transporter activators may permit the withdrawal of the increased glutamate in the synaptic cleft into the surrounding glial cells.

The time of therapeutic intervention is also of major importance. Glutamate excitotoxicity involves a cascade of events starting from the over-activation of the glutamate receptors and ending with neuronal death. This cascade of events lasts for 24 hours and may extend to 72 hours. Accordingly, the therapeutic intervention should be as soon as possible. Several studies have shown that the exposure to traumatic brain injury, ischemia or stroke induces a massive increase in glutamate release followed by the influx of Ca^{2+} ions and production of free radicals and finally neuronal death. This is followed by a latent period through which no signs or symptoms appear and nerve outgrowth takes place to compensate the neuronal losses - a phenomenon known as nerve sprouting. This period may take several years after which the symptoms start to appear depending on the site of lesion. This may take the form of epilepsy, Parkinson's disease or dementia. Accordingly the persons exposed to traumatic brain injury during birth should be closely observed. Moreover, cautions should be taken to avoid insults that induce massive glutamate release such as ischemia, stroke and trauma. The therapeutic intervention in such cases should be as fast as possible to prevent the cascade of glutamate excitotoxicty. In addition, people with low threshold of excitability such as epileptic patients should avoid exposure to environmental pollutants that affect glutamatergic activity.

References

1. Farso MC, O'Shea RD, Beart PM (2009) Evidence group ImGluR drugs modulate the activation profile of lipopolysaccharide- exposed microglia in culture. Neurochem Res 34: 1721-1728.
2. Saransaari P, Oja SS (2010) Mechanisms of inhibitory amino acid release in the brain stem under normal and ischemic conditions. Neurochem Res 35: 1948-56.

3. Fairman WA, Amara SG (1999) Functional diversity of excitatory amino acid transporters: ion channel and transport modes. Am J Physiol 277: 481-486.

4. Gao SF, Bao AM (2011) Corticotropin-releasing hormone, glutamate, and γ-aminobutyric acid in depression. Neuroscientist 17: 124–144.

5. Attwell D, Laughlin SB (2001) An energy budget for signaling in the grey matter of the brain. J Cereb Blood Flow Metab 21: 1133–1145

6. Gagliardi RJ (2000) Neuroprotection, excitotoxicity and NMDA antagonists. Arquivos de Neuro-Psiquiatria 58: 583–588.

7. Mattson M (2003). Excitotoxic and excitoprotective mechanisms: abundant targets for the prevention and treatment of neurodegenerative disorders. Neuromolec Med 3: 65-94.

8. Tsai G, Coyle JT (2002). Glutamatergic mechanisms in schizophrenia. Ann Rev Pharmacol Toxicol 42: 165-179.

9. Wang Y, Qin ZH (2010) Molecular and cellular mechanisms of excitotoxic neuronal death. Apoptosis 15: 1382-1402.

10. Carafoli E, Santella L, Branca D, Brini M (2001) Generation, control, and processing of cellular calcium signals. Crit Rev Biochem Mol Biol 36: 107– 260.

11. Mody I, MacDonald JF (1995) NMDA receptor-dependent excitotoxicity: the role of intracellular Ca2+ release. Trends in Pharmacological Sciences 16: 356–359.

12. Nicholls DG (2004) Mitochondrial dysfunction and glutamate excitotoxicity studied in primary neuronal cultures. Curr Mol Med 4:149–177

13. Fiskum G, Starkov A, Polster BM, Chinopoulos C (2003) Mitochondrial mechanisms of neural cell death and neuroprotective interventions in Parkinson's disease. Ann N Y Acad Sci 991: 111–119

14. Zhang Y, Wang H, Li J, Jimenez DA, Levitan ES, Aizenman E, Rosenberg PA (2004) Peroxynitrite-induced neuronal apoptosis is mediated by intracellular zinc release and 12-lipoxygenase activation. J Neurosci 24: 10616–10627.

15. Lau A, Arundine M, Sun HS, Jones M, Tymianski M (2006) Inhibition of caspasemediated apoptosis by peroxynitrite in traumatic brain injury. J Neurosci 26: 11540–11553.

16. Khashaba MT, Shouman BO, Shaltout AA, Al-Marsafawy HM, Abdel-Aziz MM, Patel K, Aly H (2006) Excitatory amino acids and magnesium sulfate in neonatal asphyxia. Brain Dev 28: 375-379.

17. Doherty J, Dingledine R (2002) The roles of metabotropic glutamate receptors in seizures and epilepsy. Current Drug Targets: CNS and Neurological Disorders 1: 251–260.

18. Chapman AG (2000) Glutamate and epilepsy. J Nutr 130: 1043S–1045S.

19. Parameshwaran K, Dhanasekaran M, Suppiramaniam V (2008) Amyloid beta peptides and glutamatergic synaptic dysregulation. Exp Neurol 210: 7-13.

20. Hynd MR, Scott HL, Dodd PR (2004) Glutamate mediated excito toxicity and neurodegeneration in Alzheimer's disease. Neurochem 45: 583-595.

21. Velliquette RA, O'Connor T, Vassar R (2005) Energy inhibition elevates beta-secretase levels and activity and is potentially amyloidogenic in APP transgenic mice: possible early events in Alzheimer's disease pathogenesis. J Neurosci 25: 10874-10883

22. El-faramawy YA, El-banouby MH, Sergeev P, Mortagy AK, Amer MS et al. (2009) Changes in glutamate decarboxylase enzyme activity and tau-protein phosphorylation in the hippocampus of old rats exposed to chronic mild stress: Reversal with the neuronal nitric oxide synthase inhibitor 7-nitroindazole. Pharmacol Biochem Behav 91:339-44.

23. Obeso JA, Rodriguez-Orez MC, Benitez-Temino B, Blesa FJ, Guridi J et al. (2008). Functional organization of the basal ganglia: therapeutic implications for the treatment of Parkinson's disease. Mov Disord 23: S548–S559.

24. Greenamyre JT, Porter RH (1994) Anatomy and physiology of glutamate in the CNS. Neurology 44: S7–13.

25. Groom AJ, Smith T, Turski L (2003) Multiple sclerosis and glutamate. Ann NY Acad Sci 993: 229–275.

26. Sarchielli P, Greco L, Floridi A, Floridi A, Gallai V (2003) Excitatory amino acids and multiple sclerosis: evidence from cerebrospinal fluid. Arch Neurol 60: 1082–1088.

27. Vallejo-Illarramendi A, Domercq M, Perez-Cerda F, Ravid R, Matute C (2006) Increased expression and function of glutamate transporters in multiple sclerosis. Neurobiol Dis 21: 154–164.

28. Bolton C, Paul C (2006) Glutamate receptors in neuroinflammatory demyelinating disease. Med Inflamm 2006: 1–12.

29. Matute C, Domercq M, Sanchez-Gomez MV (2006) Glutamatemediated glial injury: mechanisms and clinical importance. Glia 53: 212–224.

30. Khadrawy YA , Ahmed NA, Aboul Ezz HS, Radwan NM (2009) Effect of electromagnetic radiation from mobile phone on the levels of cortical amino acid neurotransmitters in adult and young rats. Romanian J Biophys 19: 295–305.

31. Ezz HSA (2006) The chronic effect of aluminum administration on amino acid neurotransmitters in the hippocampus and hypothalamus of adult rat brain. Egypt J Zool 47: 167-181

32. Abdel-Zaher AO, Abdel-Hady RH, AbdelMoneim WM, Salim SY (2011) Alpha-lipoic acid protects against potassiumcyanide-induced seizures and mortality. Exp Toxicol Pathol 63:161–165.

33. Blaylock RL (1997) Excitotoxins: The Taste That Kills. Health Press, Santa Fe, NM, 248-254.

34. Xiong JS, Branigan D, Li M (2009) Deciphering the MSG controversy. Int J Clin Exp Med 2: 329-336

35. Danysz W, Parsons C, Möbius HJ, Stoffler A, Quack G (2000) Neuroprotective and symptomatological action of memantine relevant for Alzheimer's disease- a unified glutamatergic hypothesis on the mechanism of action. Neurotoxic Res 2: 85-97.

36. Miguel-Hidalgo JJ, Alvarez XA, Cacabelos R, Quack G (2002) Neuroprotection by memantine against neurodegeneration induced by beta-amyloid (1-40). Brain Res 958: 210-221

37. Dodd PR (2002) Excited to death: different ways to lose your neurons. Biogerontology 3: 51-56.