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Excitotoxicity as a molecular mechanism in Epilepsy

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Abstract

Excess glutamate accumulates in synapses between two neurons causing excitotoxicity. Presynaptic astrocyte mainly absorbs excess glutamate as a clearance mechanism via glutamate receptors. Excitotoxicity is related to dysfunction in mitochondria and endoplasmic reticulum and associated with age-related neurodegenerative diseases as well as stroke, epilepsy and traumatic brain injury. Identifying the underlying molecular mechanism of excitotoxicity and ways to combat it will help to stop or slow the progress of neurodegeneration.

Introduction

A number of cellular processes are observed in almost all neurodegenerative disorders such as increased oxidative stress, reactive oxygen species, mitochondrial dysfunction, lysosomal dysfunction, protein aggregation, inflammation, excitotoxicity, apoptosis, necrosis and metabolic syndrome. These processes may underlie the molecular mechanisms of neurodegeneration and enlightening the pathways may pave the way for the potential therapeutics.

Excitotoxicity is a major condition associated with age-related neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, ALS (Amyloid Lateral Sclerosis) as well as stroke, epilepsy and traumatic brain injury [1,2]. Excitotoxicty occurs as a result of the accumulation of excess glutamate in synapses. Normally, excess glutamate is absorbed by presynaptic astrocytes via the glutamate receptors on their membranes.

Glutamate functions as one of the major neurotransmitters in the Central Nervous System (CNS) [1]. It is also a precursor for GABA in neurons and glutamine in astrocytes. Glutamate controls main functions of CNS such as learning, memory, cognition and emotion linking glutamate to the physiology of CNS. Glutamate is recognized as the main excitatory amino acid transporters (EAATs) in the vertebrate CNS with up to 40% of all synapses being glutamatergic [2,3]. EAATs carry out energy-dependent glutamate transport in CNS. Three neuronal isoforms and two glial isoforms of Na-dependent glutamate transporters exist in brain and EAAT2, also known as GLT-1 is the predominant isoform in the brain [1], mostly located on astrocytes and carry out as much as 95% of glutamate transport [4-6]. This happens as a result of the normal neuronal function and protects against excitotoxicity. Therefore, brain depends on the glutamate transport performed by the EAATs and also excess glutamate to be absorbed by them, since there is no extracellular catabolic mechanism for glutamate.

Excitotoxicty also affects the mitochondria function, since excessive glutamate disrupts Ca^{+2} balance and ATP production and further leads to the formation of reactive oxygen species. It is also associated with endoplasmic reticulum stress due to the pathological Ca^{+2} signal evoked by excess glutamate.

Excitotoxicity and epilepsy

Epilepsy is a common neurological disorder affecting people of all ages and characterized by epileptic seizures. The causes of epilepsy are both genetic [7] and non-genetic. Less number of cases is due to genetic mutations. Non-genetic reasons include brain injury, brain infections, brain trauma, stroke and birth defects.

Epilepsy is associated with unpredictable seizures due to abnormal electrical activity. Excitotoxicty is one of the main reasons of these seizures since seizure activity is transmitted from one neuron to the next primarily through excitatory glutamatergic transmission. It is known that glutamate-induced excitotoxicity causes the neuronal death in epilepsy and increased glutamate levels were observed in epileptic human brain tissues and also in animal models of epilepsy [8,9]. Glutamate that is released from synapses act on ionotropic and metabotropic receptors, which afterwards leads to the initiation and transmission of the seizures [10].

Excess glutamate causing neurotoxicity is absorbed by astrocytes via glutamate transporters. Glutamate is not metabolized by any enzyme significantly. The most efficient way to remove glutamate is by receptor uptake through astrocytes [11-13]. It is then either converted to glutamine via glutamine synthetase in astrocytes or metabolized by glutamate dehydrogenase and then brought into TCA cycle. Glutamine is transported out of the astrocyte and then taken up by the glutamatergic neuron where it is converted to glutamate by glutaminase enzyme [14]. Rapid metabolism of intracellular glutamate via glutamine synthetase is a critical step for the efficient clearance of glutamate from synaptic cleft. Several studies showed that glutamine synthetase activity in astrocytes is reduced in neurodegenerative diseases, including MTLE (Median Temporal Lobe Epilepsy). The loss of glutamine synthetase activity might be the reason for the increased extracellular glutamate and epileptic seizures in MTLE [15].

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Studies characterizing excitotoxic mechanisms in epilepsy have focused on studying glutamate transporters and/or receptors. The sole mechanism for the removal of glutamate from extracellular space is via the transporter proteins. By this way, glutamate transporters preserve the non-toxic concentrations of glutamate. In addition to this, glutamate transporters modulate synaptic transmission and intersynaptic cross-talk [1]. It was shown in different studies that altering glutamate receptor or glutamate transporter expression by knockout or knockdown procedures in mouse models can induce or suppress epileptic seizures. Overstimulation of glutamate receptor causes the increased influx of Ca^{+2} and Na^{+} through ion channels, which is followed by the transport of Cl^{-} and water. Postsynaptic neurons are overloaded by extracellular Ca^{+2} and Na^{+} as well as intracellular Ca^{+2} released from mitochondria. This combined Ca^{+2} overload leads to a metabolic damage in the cell resulting in necrosis [16,17].

The mitochondrial membrane potential is disrupted by the elevated influx of Ca^{+2}, which can reduce ATP synthesis [18]. In addition, cytochrome c is released during excitotoxicity leading to a delay in mitochondrial depolarization and the production of ROS [19,20].

As stated above, overstimulation of glutamate receptors induces Ca^{+2} influx and collapse of mitochondria, leading to progressive death of neurons [21]. In addition to mitochondria, endoplasmic reticulum is another organelle that is affected from glutamate overload. Increased Ca^{+2} influx may cause disintegration of the endoplasmic reticulum membrane, resulting in endoplasmic reticulum stress and ROS generation, which will eventually lead to apoptosis and necrosis in neurons [22].

Necrosis is initially accepted as a mechanism of cell death after excitotoxicity. Necrosis is non-programmed passive cell death. It happens as a result of cell swelling and autolysis. It was shown that some neurons may die as a result of apoptosis, programmed cell death, after excitotoxicity [23]. Basically, neurons mainly die as a result of necrosis after being exposed to excitotoxic concentrations of glutamate. Surviving neurons may undergo delayed apoptosis. Complex cellular processes such as decrease in synaptic plasticity, disruption of neuronal circuitry, changes in interneuron number occur due to a massive neuronal death. These events cause epileptogenic changes leading to the development of spontaneous seizures. Reducing glutamate-mediated excitotoxicity may help to stop or decrease seizure-induced epileptogenesis. Since apoptosis and necrosis are the two pathways that neurons die as a result of excitotoxicity in epilepsy, investigating molecules that will interfere with these pathways to prevent neuronal death will be an interesting area for research for this condition.

Another promising area to develop therapeutics for preventing excitotoxicity is glutamate transporters. The glutamate transporter EAAT2 (GLT-1) in glia plays a major role in glutamate uptake. Dysfunction or reduced expression of EAAT2 is observed in various neurodegenerative diseases or conditions. Many experimental studies with animal models demonstrated that increased EAAT2 expression prevents excitotoxicity. EAAT2 might be a potential target to prevent excitotoxicity. EAAT2 might be upregulated via transcription, translation or activators can be designed for trials [24].

Kainic acid is used mainly to induce excitotoxicity in animal models of neurodegenerative diseases. The symptoms of excitotoxicity occurring in rodent models as a result of kainic acid treatment are seizures, neurodegeneration, behavioral phenotypes, oxidative stress, inflammation, endoplasmic reticulum stress, mitochondrial dysfunction. Therefore, kainic acid is used as an effective model for epilepsy both in rodents [25] and also in cell models [26].

Conclusion

Glutamate-dependent excitotoxicity is observed in almost all brain disorders and age-related neurodegenerative diseases. It is one of the main molecular mechanisms underlying epilepsy. The major pathway to prevent excitotoxicity is to remove excess glutamate from extracellular space via glutamate transporters. Therefore, developing therapeutics via activating glutamate transporters will be promising in the future in order to pave the way for combating epilepsy.

References

1. Danbolt NC (2001) Glutamate uptake. *Prog Neurobiol* 65: 1-105. [Crossref]
2. Choi DW (1988) Glutamate neurotoxicity and diseases of the nervous system. *Neuron* 1: 623-634. [Crossref]
3. Shih J, Liu L, Mason A, Higashimori H, Donmez G (2014) Loss of SIRT4 decreases GLT-1-dependent glutamate uptake and increases sensitivity to kainic acid. *J Neurochemistry* 131(5): 573-81
4. Rothstein JD, Martin L, Levey AI, Dykes-Hoberg M, Jin L, et al. (1994) Localization of neuronal and glial glutamate transporters. *Neuron* 13: 713-725. [Crossref]
5. Rothstein JD, Dykes-Hoberg M, Pardo CA, Bristol LA, Jin L, et al. (1996) Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. *Neuron* 16: 675-686.
6. Conti F, Weinberg RJ (1999) Shaping excitation at glutamatergic synapses. *Trends Neurosci* 22: 451-458. [Crossref]
7. Pandolfo M (2011) Genetics of epilepsy. *Semin Neurol* 31: 506-518. [Crossref]
8. Haglid KG, Wang S, Qiner Y, Hamberger A (1994) Excitotoxicity. Experimental correlates to human epilepsy. *Mol Neurobiol* 9: 259-263. [Crossref]
9. Coulter DA, Eid T (2012) Astrocytic regulation of glutamate homeostasis in epilepsy. *Glia* 60: 1215-1226. [Crossref]
10. Chapman AG (2000) Glutamate and epilepsy. *J Nutr* 130: 1043S-5S. [Crossref]
11. Balcar VJ, Johnston GA (1972) The structural specificity of the high affinity uptake of L-glutamate and L-aspartate by rat brain slices. *J Neurochem* 19(11): 2657-2666.
12. Logan WJ, Snyder SH (1972) High affinity uptake systems for glycine, glutamic and aspaspartic acids in synaptosomes of rat central nervous tissues. *Brain Res* 42(2): 413-431.
13. Johnston D, Brown TH (1981) Giant synaptic potential hypothesis for epileptiform activity. *Science* 211: 294-297. [Crossref]
14. Karaca M, Frigerio F, Maechler P (2011) From pancreatic islets to central nervous system, the importance of glutamate dehydrogenase for the control of energy homeostasis. *Neurochem Int* 59(4): 510-517.
15. Eid T, Tu N, Lee TS, Lai JC (2013) Regulation of astrocyte glutamine synthetase in epilepsy. *Neurochem Int* 63: 670-681. [Crossref]
16. 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. [Crossref]
17. Mody I, MacDonald JF (1995) NMDA receptor-dependent excitotoxicity: the role of intracellular Ca+2 release. Trends in Pharmacological Sciences 16: 356-359.
18. Park KW, Kim GE, Morales R, Moda F, Moreno-Gonzalez I, et al. (2017) The Endoplasmic Reticulum Chaperone GRP78/BiP Modulates Prion Propagation *in vitro* and *in vivo*. *Scientific Reports* 7: 44723.
19. Nicholls DG (2004) Mitochondrial dysfunction and glutamateexcitotoxicity studied in primary neuronal cultures. Curr Mol Med 29 4: 149-17713.
20. Fiskum G, Starkov A, Polster BM, Chinopoulos C (2003) Mitochondrial mechanisms of neural cell death and neuroprotective interventions inParkinson's disease. Ann N Y Acad Sci 991: 111–119.
21. McGeer EG, McGeer PL (1978) Some factors influencing the neurotoxicity of intrastriatal injections of kainic acid. *Neurochem Res* 3: 501-517. [Crossref]
22. Xue F, Shi C, Chen Q, Hang W, Xia L, et al. (2017) Melatonin Mediates Protective Effects against Kainic Acid-Induced Neuronal Death through Safeguarding ER Stress and Mitochondrial Disturbance. *Front Mol Neurosci* 10: 49. [Crossref]

23. Ankarcrona M, Dypbukt JM, Bonfoco E, Zhivotovsky B, Orrenius S, et al. (1995) Glutamate-induced neuronal death: a succession of necrosis or apoptosis depending on mitochondrial function. *Neuron* 15: 961-973. [Crossref]

24. Lin CL, Kong Q, Cuny GD, Glicksman MA (2012) Glutamate transporter EAAT2: a new target for the treatment of neurodegenerative diseases. *Future Med Chem* 4: 1689-1700. [Crossref]

25. Mohd Sairazi NS, Sirajudeen KNS, Asari MA, Muzaimi M, Mummedy S, et al. (2015) Kainic Acid-Induced Excitotoxicity Experimental Model: Protective Merits of Natural Products and Plant Extracts. *Evid Based Complement Alternat Med* 972623.

26. Verdaguer E, García-Jordà E, Jiménez A, Stranges A, Sureda FX, et al. (2002) Kainic acid-induced neuronal cell death in cerebellar granule cells is not prevented by caspase inhibitors. *Br J Pharmacol* 135: 1297-1307. [Crossref]