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Review

Excitotoxicity: Bridge to various triggers in neurodegenerative disorders

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ABSTRACT

Glutamate is one of the most prominent neurotransmitter in the body, present in over 50% of nervous tissue and plays an important role in neuronal excitation. This neuronal excitation is short-lived and is followed by depression. Multiple abnormal triggers such as energy deficiency, oxidative stress, mitochondrial dysfunction, calcium overload, etc can lead to aberration in neuronal excitation process. Such an aberration, serves as a common pool or bridge between abnormal triggers and deleterious signaling processes with which central neurons cannot cope up, leading to death. Excitotoxicity is the pathological process by which nerve cells are damaged and killed by excessive stimulation by neurotransmitters such as glutamate and similar substances. Such excitotoxic neuronal death has been implicated in spinal cord injury, stroke, traumatic brain injury, hearing loss and in neurodegenerative diseases of the central nervous system such as stroke, epilepsy, multiple sclerosis, Alzheimer disease, Amyltropic lateral sclerosis, Parkinson's disease, Huntington disease and alcohol withdrawal. This review mainly emphasizes the triggering events which sustain neuronal excitation, role of calcium, mitochondrial dysfunction, ROS, NO, chloride homeostasis and eicosanoids pathways. Further, a brief introduction about the recent research occurring in the treatment of various neurodegenerative diseases, including a summary of the presumed physiologic mechanisms behind the pharmacology of these disorders.

Contents

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1. Introduction

Excitotoxicity refers to toxic effects, resulting from excessive or prolonged activation of excitatory amino acid receptors (Lipton et al., 2008; Vincent and Mulle, 2009). For the last few decades, the excitatory amino acid neurotransmitter, glutamate, has been hypothesized to have a pivotal role in the pathogenesis of neuronal death (Bano et al., 2005). In 1969 extensive studies by Olney & Co-workers coined the term excitotoxicity which is used when excessive glutamate acts on excitatory receptor and cause cell death (Budd Haeberlein et al., 2009; Heneka et al., 2010; Munoz-Sanjuan and Bates, 2011). Glutamate, the most abundant neurotransmitter in the brain, its overstimulation increases intracellular calcium (Ca^{2+}) by directly opening post-synaptic ion

Table 1
Historical aspects of glutamate receptors and their modulators.

Year	Important events	Reference
1866	Glutamic acid was first isolated as a pure substance by German Chemist Ritthausen.	Vickery et al., 1931
1886	The identification of Monosodium Glutamate [MSG] began with the isolation of glutamic acid from a mass of wheat protein, called gluten	Fuke and Konosu (1991)
1890	The chemical structure of glutamic acid, a naturally occurring amino acid was established	Yamamoto et al., 2009
1936	The flavor enhancing ability of MSG was discovered by Japanese chemist Ikeda Kibunae	(Rolls et al., 2009)
1926	Phencyclidine which cause a certain kind of brain damage called Olney's lesions was first synthesized	Large et al., 2011
1930	Glutamate in brain was first recognized	Othmer, 1978
1940	Research on dietary glutamate and glutamine in the treatment of learning disorders and epilepsy	Jeffrey et al., 2006
1952	Phencyclidine was patented by Parke-Davis pharmaceutical company and marketed under the brand name Sernyl	Suzuki et al., 2002
1953	Kainic acid was originally isolated from the seaweed called "Kainin-sou" or" Makuri" in Japan	Moloney, 1998
1954	Glutamate as a transmitter in the mammalian CNS was described by Hayashi.	Bortolotto et al., 1994
1958	Domoic acid was originally isolated from the red alga called "doumoi" or "hanayanagi" in Japan	Hallowell et al., 2005
1960	NMDA was first synthesized as an excitotoxin	Watkins et al., 2006
1968	Monosodium Glutamate for the treatment of brain lesions and neuroendocrine disorders reported in the laboratory by John W Olney	Yamamoto et al., 2009
1966	Amantadine was approved by the US FDA as a prophylactic agent against Asian influenza	Balogh et al., 1992
1970	EAA receptors were initially classified as N-methyl-D-aspartate (NMDA) and non-NMDA receptors, the latter subdivided into quisqualate (later AMPA) and kainate receptors	Hawkins, 2009
1980	NMDA receptors were shown to be involved in several central Synaptic pathways, acting in concert with non-NMDA receptors.	Magistretti, 2009
1982	AMPA discovery by Tage Honore and Colleagues And published in the Journal of Neurology	Macdermott et al., 1986
1985	The first demonstration that glutamate could induce the formation of molecules belonging to a major second messenger system	Schoepp, 2001
1987	Existence of metabotropic glutamate receptors	Watkins et al., 2008
1989	A large family of iGluR subunits was discovered	Hollmann and Heinemann, 1994
1991	The first metabotropic glutamate receptor of the seven transmembrane domain family was cloned	Krebs, 2009
2000	A modified glutamate receptor of the brain was found, the taste -mGluR4	Nelson et al., 2002
2005	Orthosteric and allosteric modulators of the metabotropic glutamate receptor 1 ($mGlu_1$)	Conn et al., 2009
2006	Progress in the development of new drugs in Alzheimer's disease	Piau et al., 2011
2010	mGluR1—mGluR8 subunits were discovered	Conn et al., 2009
2011	Glutamate receptors in preclinical research on Alzheimers disease	Neng-Wei et al., 2012
2011	Recent advances in the design and development of novel negative allosteric modulators of mGlu(5)	Emmitte, 2011

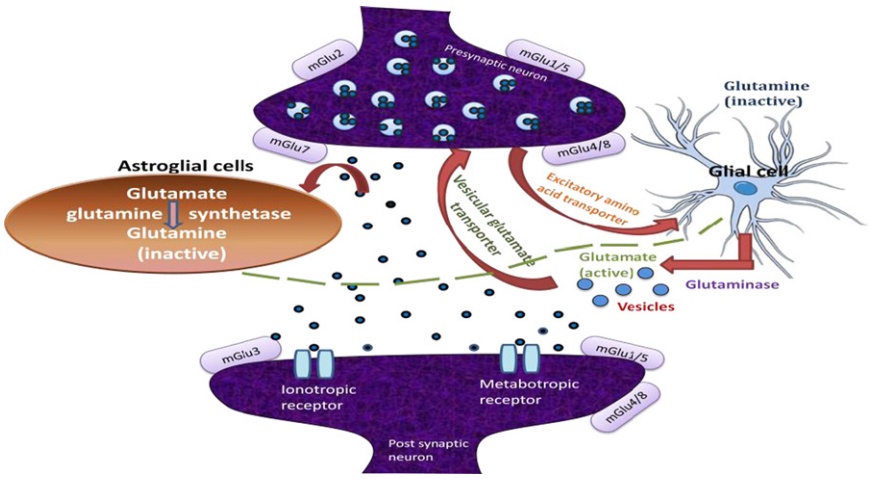

Fig. 1. Glutamate cycle in the brain The cycle shows the glutamate release from presynaptic neurons, postsynaptic neurons and from glial cells showing its point-to-point transmitter role in propagation of excitatory signals in the brain.