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REVIEW ARTICLE

Excitotoxicity Triggered by Neonatal Monosodium Glutamate Treatment and Blood–Brain Barrier Function

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It is likely that monosodium glutamate (MSG) is the excitotoxin that has been most commonly employed to characterize the process of excitotoxicity and to improve understanding of the ways that this process is related to several pathological conditions of the central nervous system. Excitotoxicity triggered by neonatal MSG treatment produces a significant pathophysiological impact on adulthood, which could be due to modifications in the blood–brain barrier (BBB) permeability and vice versa. This mini-review analyzes this topic through brief descriptions about excitotoxicity, BBB structure and function, role of the BBB in the regulation of Glu extracellular levels, conditions that promote breakdown of the BBB, and modifications induced by neonatal MSG treatment that could alter the behavior of the BBB. In conclusion, additional studies to better characterize the effects of neonatal MSG treatment on excitatory amino acids transporters, ionic exchangers, and efflux transporters, as well as the role of the signaling pathways mediated by erythropoietin and vascular endothelial growth factor in the cellular elements of the BBB, should be performed to identify the mechanisms underlying the increase in neurovascular permeability associated with excitotoxicity observed in several diseases and studied using neonatal MSG treatment.

Key Words: Excitotoxicity, Blood–brain barrier, Monosodium glutamate.

Introduction

Glutamic acid (Glu) is considered the main important excitatory neurotransmitter in the mammalian central nervous system (CNS) where it is broadly distributed and reaches elevated concentrations relative to the rest of the body (1–5). Neural signaling mediated by Glu is implicated in several physiological processes that range from sensory perception to learning (1–5), spanning motor control (6) and emotional regulation (7). At the cellular level, Glu triggers essential neuronal responses implicated in neuronal migration and differentiation, synapse remodeling and long-term potentiation (1–7). However, Glu-mediated neurotransmission is also implicated in the pathophysiology of neuronal damage. It is therefore known that excessive Glu extracellular concentrations can cause neuronal death due to excitotoxicity through a process in which overactivation of ionotropic and metabotropic Glu receptors triggers several intracellular signaling pathways that lead to apoptosis, necrosis or both (1–5). Three ionotropic Glu receptors have been identified such as N-methyl-D-Aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors (1–5). They are conformed by four protein subunits that structure a cationic central pore and are located in both pre- and postsynapsis. AMPA and kainate receptors (AMPA-R and KA-R) are quickly activated by Glu to promote the Na^+ entry. NMDA receptors (NMDA-R)

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are slowly activated (generally after non-NMDA receptors) due to the fact that they require an electrotonic depolarization of the membrane to eliminate the blocking that Mg^{2+} exerts into the pore; Ca^{2+} and Na^{+} may then cross the pore (2–5). Electrophysiological and pharmacological properties of ionotropic receptors are determinate by the subunits that compound them. AMPA-R may be composed by tetrameric arrays of GluR1-4 subunits; KA-R by GluR5-7 and KA1-2; and NMDA-R by NR1-3, all expressed in molecular variants that increase the functional possibilities of ionotropic Glu receptors (2–5). Additionally, eight metabotropic Glu receptors (mGluR1-8) subdivided in three groups have been described. Group I includes mGluR1 and mGluR5, which are located postsynaptically and activate to Gq protein, stimulating to phospholipase C and increasing intracellular formation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). Group II formed by mGluR2 and mGluR3, and group III by mGluR4 and mGluR6-8 are located presynaptically and activate to a G protein that inhibits adenylyl cyclase (2,4,5) (Figure 1). Ionotropic and group I metabotropic Glu receptors mediate excitatory effects of the neurotransmitter and also its toxic effects through overproduction of free radicals, overload of Ca^{2+} cytosolic, energetic failure and activation of several enzymes. It must also be considered that astrocytes (8), microglial cells (9) and brain endothelial cells (10) express Glu receptors and then they may be susceptible to toxic Glu effects. Several conditions involving neuronal damage have been associated with excitotoxicity including acute processes such as hypoxia-ischemia and degenerative processes such as Alzheimer's disease among other conditions (2–5). Although various specific glutamatergic agonists can mimic the toxic effects of Glu, monosodium glutamate (MSG) is possibly the most common agent that has been used to characterize the cellular and molecular mechanisms involved in excitotoxicity (1,2). This popularity could be due to the fact that MSG induces overactivation of all types of glutamatergic receptors present in CNS, which is similar to the effects that occur *in vivo*; moreover, *in vivo* administration of MSG permits researchers to temporally follow the degenerative process triggered by an excitotoxic stimulus. Furthermore, for the past several years, it has been known that neuronal

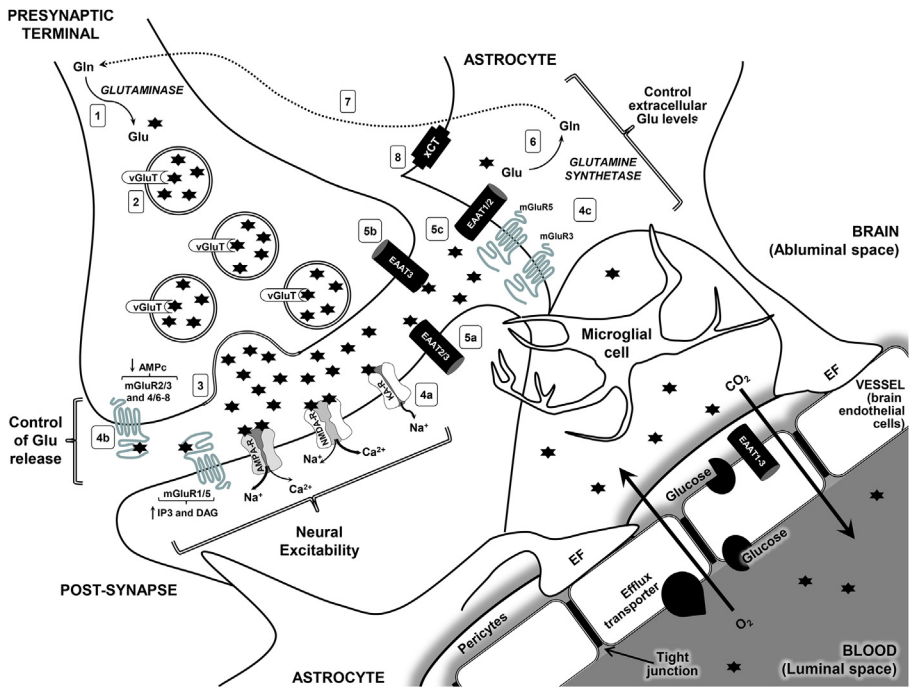

Figure 1. Scheme represents the main cellular components involved in a glutamatergic synapse and at the blood–brain barrier (BBB) in physiological conditions. At presynaptic terminal, Glu neurotransmitter synthesis is realized mainly by glutaminase (1), and then vGlu transporters introduce Glu to synaptic vesicles (2), which by exocytosis release Glu (3) when a depolarizing stimulus arrives at the synaptic terminal. In extracellular space, Glu diffuses to interact with its specific receptors at postsynapse (AMPA-R, KA-R, NMDA-R, and mGluR1 and mGluR5) (4a); at presynapse (mGluR2/3 and mGluR4/6-8) (4b) and at astrocytes (mGluR3 and mGluR5) (4c). Extracellular Glu concentration is regulated mainly by EAAT3 at neural level (5a–b) and EAAT1/2 at astrocyte level (5c). Inside the astrocyte, Glu is degraded to Gln by glutamine synthetase (6); later Gln may be transported to glutamatergic synapse (7) to promote the Glu synthesis. Furthermore, xCT transporter at astrocyte (8) may influence Glu extracellular concentration. Although, in the scheme, microglial cells close to synapses membrane proteins are not represented, it is known that Glu receptors and EAATs are also expressed in this cellular type. At the bottom right square, the BBB components [brain endothelial cells with continuous tight junctions, astroglial endfeet (EF), pericytes, microglia, and neurons], and the major general transport mechanisms localized at brain endothelial level are represented. Interactions described here are significantly modified under pathological conditions.