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The Molecular Mechanisms of Magnesium Neuroprotection in Patients with Eclampsia: A Short Review

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Eclampsia has been studied extensively over the last decades. Several pathophysiological mechanisms and animal models have been proposed for the disease. However, to date, none of them can fully explain the neuronal pathophysiology of eclamptic convulsions and the associated deleterious complications. Magnesium is the drug of choice for the prophylaxis and treatment of eclampsia in addition to prompt delivery. There is evidence to suggest that the beneficial effect of magnesium is exerted via modulation of the N-Methyl-D-Aspartate Receptor (NMDAR). The aim of this review is to explore the molecular mechanism by which magnesium exerts its neuroprotective effect and prevents eclamptic convulsions through the NMDAR activation pathway. Future investigations and alternative treatments are discussed.

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ABBREVIATIONS

CNS – Central Nervous System; NMDAR – N-Methyl-D-Aspartate Receptor.

1. INTRODUCTION

Since the ancient Egyptian era it has been known that pregnancies can be endangered by convulsions. Later in the course of history, Hippocrates noted that the combination of headaches, convulsions, and drowsiness (up to coma) is a serious complication of pregnancy. Eclampsia is the occurrence of convulsions or coma, unrelated to other cerebral conditions, in the presence of signs and symptoms of preeclampsia: hypertension and proteinuria that may be accompanied by headache, blurred vision, edema, abdominal pain, hyperreflexia and/or organ failure.

In the Western world, the reported incidence of eclampsia is about 1/2000–3448 pregnancies. Prevalence is higher in multiple pregnancy and in populations lacking prenatal care [1]. Prompt delivery of pregnant women with convulsions favors their recovery and can be lifesaving.

The pathogenesis of eclamptic convulsions is still unknown. Several mechanisms have been suggested as possible etiologic factors, but none have been conclusively proven. It is not clear whether the pathologic features in eclampsia are a cause or an effect of the convulsions.

Morriss et al. [2] and Zeeman et al. [3] have proposed several hypotheses, which were reviewed extensively and updated by Euser and Cipolla [4]:

i. *N*-methyl-D-aspartate receptor (NMDAR) reduced activation threshold resulting in increased influx of cations. This increased influx may lead to an excessive generation of action potentials. If it occurs, for example, in the motor cortex, convulsions may ensue.
ii. Cerebral overregulation, in response to high systemic blood pressure, results in vasospasm of cerebral arteries, underperfusion of the brain, localized ischemia/infarction, and cytotoxic (intracellular) edema in various brain regions.
iii. Loss of autoregulation of cerebral blood flow, in response to high systemic pressure (i.e., hypertensive encephalopathy), results in hyperperfusion, endothelial damage, and vasogenic (extracellular) edema in various regions.

Magnesium is considered to be superior to the traditional antiepileptic drugs for eclampsia prevention and for attenuation of eclamptic seizures [5]. Magnesium administration is recommended to all women with severe preeclampsia. However, the risk-benefit and cost-effectiveness of magnesium administration to women with mild preeclampsia are yet to be determined [6,7]. It is believed that magnesium may play a significant role in all the above proposed mechanisms [4]. However, little is known on how magnesium increases the eclamptic seizure threshold. Magnesium is one of the physiological blockers of NMDAR [8,9]. Based on the up-to-date literature, the aim of this review is to analyze how magnesium may protect from eclamptic convulsions, and the associated deleterious outcomes, through the NMDAR activation pathway. Eclampsia outcomes and experimental neuropathophysiology models involving NMDAR in eclampsia mechanism are reviewed.

A search in Pubmed and Google Scholar for relevant publications in English through October 2014 was performed. We used the following search terms: “eclampsia”, “magnesium”, “model”, “*N*-Methyl-D-Aspartate Receptor”, and “neuroprotection”. All types of peer-reviewed publications were considered suitable. Specifically, seven original animal research studies have addressed the possible involvement of NMDAR in the pathogenesis of eclampsia. The findings of these papers are described and discussed.

2. MATERNAL AND PERINATAL OUTCOMES IN ECLAMPSIA

MacKay et al. [10] reviewed all reported pregnancy-related deaths in the United States for the years 1979 to 1992. They identified 4,024 pregnancy-related deaths. A total of 790 (19.6 percent) were considered due to preeclampsia-eclampsia, with 49 percent of them related to eclampsia. Serious, life threatening, maternal

complications occur in up to 70 percent of women with eclampsia and include abruption placentae, disseminated intravascular coagulopathy, acute renal failure, hepatocellular injury, liver rupture, intracerebral hemorrhage, transient blindness, cardiorespiratory arrest, aspiration pneumonitis, acute pulmonary edema, and postpartum hemorrhage [11-13,14]. A meta-analysis study [15] showed that women with a history of preeclampsia/eclampsia have approximately double the risk of early cardiac, cerebrovascular, peripheral arterial disease, and cardiovascular mortality later in life. Hepatocellular damage, renal dysfunction, coagulopathy, hypertension, and neurologic abnormalities typically resolve following delivery. However, brain damage from hemorrhage or ischemia may result in permanent neurologic sequelae and is the most common cause of death in patients with eclampsia [16-18].

Perinatal mortality and morbidities are still high in pregnancies complicated by eclampsia, where 5.6 to 11.8 percent result in perinatal death, mostly related to premature delivery and abruptio placentae [13]. Perinatal mortality and morbidity are closely related to gestational age [19]. For example, perinatal mortality was 9 percent following delivery at around 32 weeks of gestation [20] but was as high as 93 percent following delivery prior to 28 weeks of gestation [21].

3. MAGNESIUM AND NMDAR IN ECLAMPSIA

Although eclampsia may be complicated with several life-threatening conditions, and despite decades of intensive research, there is still no cure except prompt delivery and supportive treatments that include parenteral magnesium administration. It has been shown that magnesium sulphate administration to eclamptic women is protective both to the pregnant woman and her fetus [5,22]. Magnesium was shown to be effective in blocking the epileptiform activity occurring in eclampsia. Magnesium is better than conservative antiepileptic drugs and is recommended for eclampsia prophylaxis and treatment [5,22,23]. The mechanism mediating magnesium's effect involves generalized central nervous system (CNS) depression, which serves to attenuate seizures. Specifically, magnesium is a physiological blocker of the excitatory NMDAR in the CNS.

NMDARs are ligand gated ion channels opened by the major excitatory neurotransmitter in the mammalian CNS, glutamate, and by its co-agonist, glycine. Most NMDARs appear to function as hetero-tetramer assemblies, composed of two dimers containing a GluN1 subunit in combination with a GluN2 subunit – a "dimer of dimers" structure [24] (Fig. 1). Magnesium ion resides in the channel pore and serves as a physiological blocker. These receptors are widespread in the CNS and are involved in numerous physiological and pathological processes including synaptic plasticity, learning, memory, chronic pain, and psychosis [25,26]. Aberrant NMDAR activity plays an important role in the neuronal loss associated with ischemic insults [8,9]. Activation of this receptor requires binding of glutamate and glycine simultaneously with the removal of Mg2+ blockade by membrane depolarization (Fig. 1). These in turn gate the cationic channel that is permeable to Na+, K+, and Ca2+. Interestingly, NMDARs are endowed with multiple extracellular regulatory sites that recognize ions or small molecule ligands. Agents that target and alter NMDAR function may, thus, have therapeutic benefit for various pathologies.

As noted above, several clinical trials have shown that magnesium sulphate is superior to nimodipine and traditional anticonvulsant drugs, including phenytoin and diazepam, for the prophylaxis and treatment of eclamptic seizures [27,28]. Seizures consist of an excessive release of excitotoxic neurotransmitters including glutamate. Excessive glutamate can activate the NMDAR, leading to massive depolarization of neuronal networks and bursts of action potentials [29,30]. Several lines of evidence support the notion that magnesium may increase the seizure threshold by inhibiting NMDAR. Hallak et al. [31] showed a possible therapeutic benefit to magnesium in eclampsia through the pathway of NMDAR response attenuation. In rat brains both electrically stimulated and NMDA-induced hippocampal seizures were depressed by systemic magnesium administration: Hallak and colleagues [32] showed that intraperitoneal injections of magnesium sulphate increased the electrical threshold required to induce seizures by 34 percent. Cotton et al. [33] tested the ability of magnesium sulphate to suppress seizures when NMDA is injected intracranially. They showed that peripherally administered magnesium sulphate significantly increased the latency from the time of NMDA injection to the first seizure. The duration of the first seizure was

also significantly reduced. Even when magnesium sulphate was administered intracranially together with NMDA, similar results were observed. They also showed that centrally administered magnesium sulphate prevented seizure activity in 40 percent of the rats. Moreover, Maurois et al. [34] demonstrated a decrease in the threshold for NMDA-induced seizures in mice undergoing chronic nutritional deprivation, which was mostly reversed by magnesium administration.

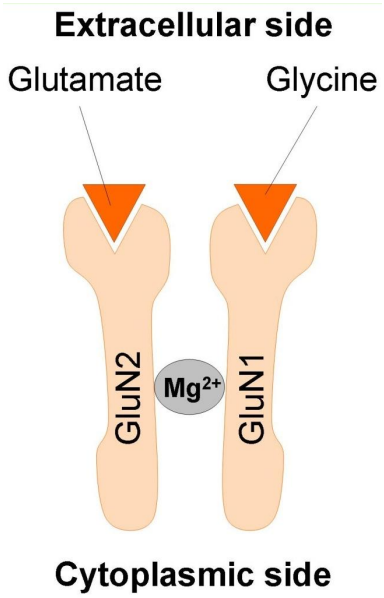

Fig. 1. NMDA receptor (NMDAR). A schematic presentation of major NMDAR subunits and ligands binding sites

To date, there are no specific CNS animal models for eclampsia. However, the penicillin-induced seizure model was studied in the context of magnesium, NMDAR, and eclampsia. In anesthetized cat cerebral cortexes, Koontz and Reid [35,36] found no significant difference in epileptic spike frequency between control animals and cats that were pre-treated with parenteral magnesium sulphate. However, in freely moving rats' sensorimotor cortex, Kryzhanovskii et al. [37] showed that addition of magnesium sulphate to benzylpenicillin sodium salt solution significantly weakened the epileptic activity. Moreover, intravenously infused magnesium sulphate reduced the epileptic neural activity induced by topical application of penicillin G to the motor cortex in anesthetized cats and dogs and in awake, undrugged primates [38]. The overall conclusion of these authors was that magnesium sulphate has a central anticonvulsant action on NMDA-induced seizures. However, none of those studies measured NMDAR ionic currents directly.

4. CONCLUSION

Eclampsia is associated with serious and potentially irreversible neurological complications. However, the complete spectrum of CNS pathophysiological changes associated with this disease is not fully understood. There is still a need to develop an appropriate experimental model for the neuronal pathophysiology in eclampsia. One of the obstacles for developing such a model is that (pre) eclampsia is a disease specific to bipedal species [39].

Magnesium sulphate is the drug of choice for eclampsia regardless of the management of prompt delivery. There is evidence that systemic administration of this drug prevents (or at least reduces) the epileptiformic convulsions in eclampsia. One of the proposed molecular mechanisms by which magnesium exerts its protective effect is attenuation of the hyperactive NMDAR responses. An animal model for eclampsia that involves different magnesium doses and direct measurement of NMDAR ionic currents has not yet been developed. In our opinion, such a model could shed much more light on the neuronal mechanism(s) by which magnesium exerts its protective and negative effects. The use of such a model may facilitate the adjustment of dosage and timing for effective and specific favorable outcome and the minimization of unwanted side effects. Further investigation of specific NMDAR blockers such as (2*R*)-amino-5-phosphonovaleric acid, MK-801, and selective NMDAR subtype modulators [40] together with a more complete understanding of the effects of magnesium may promote a safer and more efficient management of eclampsia.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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