Published in final edited form as:
Stroke. 2009 April ; 40(4): 1169–1175. doi:10.1161/STROKEAHA.108.527788.

Magnesium sulfate treatment for the prevention of eclampsia: A brief review

Anna G. Euser, PhD and **Marilyn J. Cipolla, PhD**
Departments of Neurology, Obstetrics, Gynecology & Reproductive Sciences, and Pharmacology University of Vermont College of Medicine, Burlington, VT 05405

Abstract

Background and Purpose: Magnesium sulfate is used extensively for prevention of eclamptic seizures. Empirical and clinical evidence supports the effectiveness of magnesium sulfate; however, questions remain as to its safety and mechanism. This review summarizes current evidence supporting the possible mechanisms of action and several controversies for magnesium sulfate treatment.

Summary of Review: Several mechanisms are presented, including the effects of magnesium sulfate on peripheral and cerebral vasodilation, blood-brain barrier protection, and as an anticonvulsant.

Conclusions: Though the specific mechanisms of action remain unclear, the effect of magnesium sulfate in the prevention of eclampsia is likely multi-factorial. Magnesium sulfate may act as a vasodilator, with actions in the peripheral vasculature or the cerebrovasculature, to decrease peripheral vascular resistance and/or relieve vasoconstriction. Additionally, magnesium sulfate may also protect the blood-brain barrier and limit cerebral edema formation, or it may act through a central anticonvulsant action.

Keywords

Eclampsia; Magnesium sulfate; Vasodilation; Blood-brain barrier; Anticonvulsant

Introduction

Magnesium sulfate ($MgSO_4$) has been used throughout the 20th century for prevention of eclamptic seizures[1, 2] and continues to be used extensively[3-5]. Empirical evidence supports the effectiveness of $MgSO_4$ in preventing and treating eclamptic seizures[1, 6-8], in addition to recent controlled clinical trials[5, 9, 10]. For eclamptic seizure prophylaxis in preeclamptic women, $MgSO_4$ is superior to phenytoin[11, 12], nimodipine[13], diazepam[14], and placebo[9]. In the multinational Collaborative Eclampsia Trial, $MgSO_4$ reduced the risk of recurrent seizures in eclamptic women by 52% when compared to diazepam and by 67% when compared to phenytoin[15]. The publication of these clinical trials significantly increased the use of magnesium sulfate versus other anticonvulsants in the United Kingdom and Ireland where the

Corresponding Author: Marilyn J. Cipolla, PhD University of Vermont, Dept. of Neurology 89 Beaumont Ave., Given C454 Burlington, VT 05405 Phone: (802)-656-9714 Fax: (802)-656-8704 Email: Marilyn.Cipolla@uvm.edu.

Author Disclosures
Anna G. Euser: Research Grant: AHA Northeast Affiliate Predoctoral Fellowship, Amount: >= $10,000
Marilyn J. Cipolla: Research Grant: NIH NS045849, Amount: >= $10,000
AHA EI 0540083, Amount: >= $10,000

Conflicts of Interest and Disclosures: None.

reported use in preeclampsia increased from 2% to 40%[16]. In addition, 60% of providers surveyed indicated they would use magnesium as an anticonvulsant for eclampsia in 1998, up from only 2% of eclamptic women who received magnesium sulfate in 1992[16, 17].

Although the effectiveness of $MgSO_4$ in treating and preventing eclampsia has been established, questions still exist as to its safety. There are concerns regarding the possibility of hypermagnesemia toxicity in eclampsia treatment. Normal serum concentrations of Mg^{+2} are 1.5-2.5 mEq/L (1.8-3.0 mg/dL), with one-third to one-half bound to plasma proteins[18, 19]. Total magnesium serum concentrations advocated for the treatment of eclamptic convulsions are 3.5-7 mEq/L (4.2-8.4 mg/dL)[2, 20, 21], which can be obtained by administering it intramuscularly (6 g loading dose followed by 2 g/h), intravenously (2-4 g dose up to 1 g/min) or a combination of both[6, 18, 22]. Areflexia, particularly loss of the patellar deep tendon reflex, has been observed at 8-10 mEq/L, and respiratory paralysis seen at >13 mEq/L[6, 18, 22]. Progressively higher serum magnesium levels can ultimately lead to cardiac arrest[18, 22, 23]. Some suggest that using standard infusion protocols may not lead to therapeutic serum magnesium levels in all patients, with 36.2% of patients found to have total serum magnesium lower than 4 mEq/L at 30 minutes after treatment initiation in one study[24], though no eclamptic seizures were reported during $MgSO_4$ treatment. In addition, there are reports that in some patients eclamptic seizures do not cease even with elevated levels of $MgSO_4$[6, 7, 25], suggesting that $MgSO_4$ is not effective in treating all cases of eclampsia.

As technologic advances allow for ionized magnesium to be more readily measured, questions have arisen as to whether it is more appropriate to monitor total serum magnesium or the ionized, physiologically active, form. Studies have shown little correlation between total and ionized magnesium levels, either at baseline prior to treatment or during $MgSO_4$ treatment for preeclampsia[19, 24]. In preeclamptic patients treated with a loading dose of 4 g intravenously followed by 2 g per hour infusion, it was found that both total and ionized Mg^{+2} concentrations increased quickly after infusion, but steady-state concentrations for total magnesium were 4.84 ± 0.24 mg/dL, whereas for ionized magnesium it was 2.04 ± 0.14 mg/dL[19]. Similar results have been found by other groups using the same infusion protocol[24]. Interestingly, as $MgSO_4$ infusion caused significant increases in ionized Mg^{+2} levels, serum ionized calcium (Ca^{+2}) concentrations were unchanged[26], suggesting that the effect of $MgSO_4$ is not exerted through modulations of ionized calcium levels.

Though the use of $MgSO_4$ is wide-spread and effective, its mechanism of action remains unclear. Several possible mechanisms of action have been proposed, including acting as a vasodilator, with actions either peripherally or in the cerebral circulation to relieve vasoconstriction, protecting the blood-brain barrier (BBB) to decrease cerebral edema formation, and acting as a central anticonvulsant. Each of these possible mechanisms of action are discussed below.

Magnesium-induced Vasodilation

Magnesium is a unique calcium antagonist as it can act on most types of calcium channels in vascular smooth muscle[27] and as such would be expected to decrease intracellular calcium. One major effect of decreased intracellular calcium would be inactivation of calmodulin-dependent myosin light chain kinase activity and decreased contraction[27], causing arterial relaxation that may subsequently lower peripheral and cerebral vascular resistance, relieve vasospasm, and decrease arterial blood pressure. The vasodilatory effect of $MgSO_4$ has been investigated in a wide variety of vessels. For example, both *in vivo* and *in vitro* animal studies have shown that it is a vasodilator of large conduit arteries such as the aorta[28, 29], as well as smaller resistance vessels including mesenteric[27, 30-32], skeletal muscle[27], uterine[33], and

cerebral arteries[27, 30, 34]. However, the importance of magnesium-induced vasodilation in the treatment and prevention of eclampsia is not completely understood.

The theory of cerebrovascular vasospasm as the etiology of eclampsia seemed to be reinforced by transcranial Doppler (TCD) studies which suggested that $MgSO_4$ treatment caused dilation in the cerebral circulation[35-37] as well as in animal studies that used large cerebral arteries[34]. However, a vasodilator such as $MgSO_4$ would seem to be a paradoxical treatment choice for eclamptic encephalopathy. Eclampsia is thought to be a form of posterior reversible encephalopathy syndrome (PRES) and similar to hypertensive encephalopathy, in which acute elevations in blood pressure cause forced dilatation of the myogenic vasoconstriction of cerebral arteries and arterioles, increased BBB permeability and edema formation[38-40]. Studies from our lab have shown that $MgSO_4$ causes concentration-dependent vasodilatation in both cerebral and mesenteric resistance arteries; however, mesenteric arteries were significantly more sensitive to $MgSO_4$, particularly during pregnancy[30]. The finding of a modest vasodilatory effect in the cerebral circulation are consistent with other findings that $MgSO_4$ treatment caused no significant change in cerebral blood flow (CBF), large cerebral artery diameter, or mean middle cerebral artery velocity as determined by magnetic resonance imaging (MRI)[41] and TCD[42, 43]. Together, these results suggest that the effects of $MgSO_4$ as an eclamptic seizure prophylaxis may be more closely related to an effect on peripheral vascular resistance and lowering of systemic blood pressure than to a direct effect on CBF (Table 1 and Figure 1).

Reports of the effects of $MgSO_4$ treatment on arterial blood pressure have been mixed. Hypotensive effects have been noted in various studies particularly with bolus injections[2, 36, 44], though the duration of decreased blood pressure was varied. In pregnant rats treated with the nitric oxide synthase inhibitor L-NAME to induce hypertension, combination treatment with $MgSO_4$ resulted in significantly lower blood pressures at term and better neonatal outcomes versus animals treated with L-NAME alone[45]. However, it has been cautioned that $MgSO_4$ should not be considered primarily an anti-hypertensive agent, as there are other drugs better suited for that purpose in eclampsia, including hydralazine, labetalol, and nifedipine [20, 22].

Several reports have suggested that gestation may influence vascular reactivity to $MgSO_4$ and that sensitivity varies with vascular bed[28-30, 33]. Human uterine arteries from pregnant patients are three-fold more reactive to $MgSO_4$ than uterine arteries from non-pregnant patients[33]. In aorta from pregnant and non-pregnant rats, both increased and decreased sensitivity to $MgSO_4$-induced vasodilation have been shown based on the preconstriction agent used for *in vitro* studies. These studies also suggest that pregnancy may differentially affect receptor versus voltage-operated calcium channels in aortic smooth muscle[28]. In another study of rat aortic rings, the effect of $MgSO_4$ was dependent on gestation and nitric oxide production such that vasodilation was less at term than during late pregnancy[29]. Our studies found that while mesenteric resistance arteries showed no change in sensitivity with gestation, posterior cerebral resistance arteries from late-pregnant and postpartum animals were significantly less sensitive to $MgSO_4$-induced vasodilation versus those from nonpregnant animals[30]. This may be due to gestation-induced changes in the cerebral endothelial vaodilatory mechanisms that have been demonstrated during pregnancy and the postpartum state[46].

$MgSO_4$ may have other effects within the vasculature that could also explain its effectiveness in eclampsia (included in Figure 1). Magnesium may act by stimulating production of prostacyclin by endothelial cells causing vasodilation[47], or by inhibiting platelet aggregation[47, 48]. In patients with pregnancy-induced hypertension, $MgSO_4$ treatment significantly decreased circulating levels of angiotensin-converting enzyme[49]. These actions may attenuate the endothelial dysfunction associated with (pre)eclampsia[50-52].

Effects on the Blood-brain Barrier and Cerebral Edema Formation

The cerebral endothelium that forms the BBB has unique features compared to the peripheral endothelium including a lack of capillary fenestrations[53], a low basal rate of pinocytosis[54, 55], and the presence of high electrical resistance tight junctions between adjacent endothelial cells[54, 56]. Disruption of the BBB can result in vasogenic edema formation, an important component in the clinical picture of eclampsia[57, 58]. Decreased BBB permeability with $MgSO_4$ treatment has been reported in a variety of animal models of BBB disruption including traumatic brain injury[59], septic encephalopathy[60], hypoglycemia[61], and mannitol injection[62]. We recently reported $MgSO_4$ treatment decreased BBB permeability in response to acute hypertension in late-pregnant rats[63]. In addition, several studies have shown that $MgSO_4$ decreases cerebral edema formation after brain injury[59, 62, 64-67]. Together, these studies importantly suggest that one mechanism by which $MgSO_4$ is effective in eclampsia treatment may be through protection of the BBB and decreased cerebral edema formation.

Several mechanisms of action have been proposed to explain the neuroprotective effects of $MgSO_4$ (Table 2 and Figure 2). Magnesium is a calcium antagonist that acts both intracellularly and extracellularly[68], and may act directly on cerebral endothelial cells. It is possible that by acting as a calcium antagonist at the level of the endothelial cell actin cytoskeleton, $MgSO_4$ opposes paracellular movement of solutes through the tight junctions (Figure 2). This hypothesis is supported by several studies which demonstrated that inhibition of myosin light chain (MLC) phosphorylation decreases agonist-induced permeability by inhibiting actin stress fiber contraction[69-71]. Alternatively, pinocytosis is induced by acute hypertension and may contribute to increased BBB permeability during elevated intravascular pressure.[72] $MgSO_4$ treatment may therefore decrease pinocytosis caused by acute hypertension and restrict the movement of water and solutes into the brain by transcellular transport, thereby limiting edema formation and improving clinical outcomes in eclampsia.

Anticonvulsant Activity

Although widely used, there is controversy regarding the use of $MgSO_4$ treatment for neurological conditions, such as eclamptic seizures. Concerns have been raised that $MgSO_4$ treatment may mask the outward signs of convulsions through its action at the neuromuscular junction without treating the cause of the seizure in the central nervous system[18, 73]. Dose-related depression of neuromuscular transmission has been shown in preeclamptic women receiving traditional $MgSO_4$ therapy[74]. Studies have also shown that there is little to no change in electroencephalograms obtained during $MgSO_4$ treatment, and minimal signs of central nervous system depression in both normal[75] and eclamptic patients[25], and in animals[76]. However, clinical trials have demonstrated the efficacy of $MgSO_4$ in the treatment and prevention of eclamptic seizures versus more traditional anticonvulsant drugs, including phenytoin and diazepam [12, 14, 15].

The possible anticonvulsant activity of magnesium may be related to its role as an N-methyl-D-aspartate (NMDA) receptor antagonist[77-79], shown in Table 3 and Figure 3. Seizures are thought to be mediated at least in part by stimulation of glutamate receptors, such as the NMDA receptor[79, 80]. In rats, systemic magnesium treatment results in a resistance to both electrically stimulated[81] and NMDA-induced hippocampal seizures[82]. In addition, systemic treatment with $MgSO_4$ causes a significant reduction in the NMDA receptor binding capacity in the brain[78]. Animal studies have also shown that $MgSO_4$ reduces epileptic seizure activity[83], though these findings have been challenged due to inadequate controls[76].

Magnesium ions must cross the BBB in order to elicit a central anticonvulsant effect. It has been demonstrated in animals that $MgSO_4$ can cross the intact BBB and enter the central nervous system in correlation with the level of serum hypermagnesemia[81]. Interestingly,

seizure activity increases the movement of magnesium into the brain[81]. Human studies have also shown small but significant increases in cerebrospinal fluid concentrations of $MgSO_4$ after systemic administration[2, 84]. Conversely, other work has suggested that the BBB prevents changes in brain and cerebrospinal fluid magnesium concentrations[85]. However, this same group later suggested that even a small amount of magnesium in the central nervous system may suppress cortical neuronal activity[86]. The possibility remains that acute hypertension that leads to convulsions and BBB disruption may permit $MgSO_4$ to enter the brain parenchyma and act as an anticonvulsant during eclampsia.

Future Directions

A better understanding of the mechanisms of action of $MgSO_4$ could allow for more directed use in the treatment of eclampsia and other brain injury disorders. An interesting area for future studies is the relationship between $MgSO_4$ and cerebral edema formation, as it has been proposed that $MgSO_4$ may limit cerebral edema formation through an effect on aquaporin (AQP) expression. Aquaporin-4 (AQP4) is a water channel protein that has been localized to astrocytic endfeet[87, 88] and has also been reported to have a perivascular domain[89]. Cerebral edema in response to brain injury is associated with an upregulation of AQP4 in the brain[90, 91], and it has been suggested that $MgSO_4$ treatment attenuates cerebral edema formation via downregulation of AQP4 expression in astrocytes[65], though the mechanism of action has not been delineated. This idea is particularly interesting with respect to eclampsia as cerebral AQP4 expression is significantly increased during pregnancy[92].

One of the difficulties in studying preeclampsia and eclampsia is the lack of appropriate animal models, particularly as (pre)eclampsia is a disease specific to bipedal species[93]. In our lab, we have used a rat model of hypertensive encephalopathy during pregnancy to study the neurologic outcomes of eclampsia, specifically how acute elevations in blood pressure lead to forced dilatation of myogenic vasoconstriction, causing increased blood-brain barrier permeability and subsequent edema formation[63, 94]. Other animal models of preeclampsia and eclampsia exist, including reduced uterine placental perfusion (RUPP), Dahl Salt-Sensitive rats, nitric oxide synthase inhibition, and exogenous soluble fms-like tyrosine receptor kinase-1 (sFlt-1). These models focus on different aspects of the disease including the impact of placental perfusion, preexisting hypertension, and the significance of endothelial dysfunction, oxidative stress and circulating anti-angiogenic factors. The pros and cons of the different models have been reviewed elsewhere[93, 95], all of which provide opportunities to further study the specific actions of $MgSO_4$ for seizure prophylaxis.

Conclusion

$MgSO_4$ has been shown to be an effective treatment option for the prevention of eclampsia. Its mechanism of action is likely multi-factorial, encompassing both vascular and neurological mechanisms. Being a calcium antagonist, its effect on vascular smooth muscle to promote relaxation and vasodilation may have a role in lowering total peripheral vascular resistance. In addition, $MgSO_4$ may have an effect on the cerebral endothelium to limit vasogenic edema by decreasing stress fiber contraction and paracellular permeability via calcium-dependent second messenger systems such as MLC kinase. Lastly, $MgSO_4$ may also act centrally to inhibit NMDA receptors, providing anticonvulsant activity by increasing the seizure threshold. A more complete understanding of the effects of $MgSO_4$ will likely promote safer and more effective treatments of eclampsia.

Acknowledgements and Funding

We gratefully acknowledge the support of the American Heart Association Established Investigator Award (0540081N to M.J.C.), the American Heart Association Northeast Affiliate Research Committee Predoctoral Fellowship

(000019871 to A.G.E.), the National Institute of Neurological Disorders and Stroke (R01 NS045940 to M.J.C.), the Totman Medical Research Trust, and the University of Vermont College of Medicine MD/PhD Program.

References

1. Lazard EM. A preliminary report on the intravenous use of magnesium sulfate in puerperal eclampsia. Am J Obstet Gynecol 1925;9:178–188.
2. Pritchard JA. The use of the magnesium ion in the management of eclamptogenic toxemias. Surg Gynecol Obstet 1955;100:131–140. [PubMed: 13238166]
3. Working Group on High Blood Pressure in Pregnancy. National high blood pressure education program working group report on high blood pressure in pregnancy. Am J Obstet Gynecol 1990;163:1689–1712.
4. Sibai BM. Magnesium sulfate is the ideal anticonvulsant in preeclampsia-eclampsia. Am J Obstet Gynecol 1990;162:1141–1145. [PubMed: 2288560]
5. Witlin AG, Sibai BM. Magnesium sulfate therapy in preeclampsia and eclampsia. Obstet Gynecol 1998;92:883–889. [PubMed: 9794688]
6. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: Evalauation of 235 cases. Am J Obstet Gynecol 1984;148:951–960. [PubMed: 6711634]
7. Sibai BM, McCubbin JH, Anderson GD, Lipshitz J, Dilts PV Jr. Eclampsia. I. Observations from 67 recent cases. Obstet Gynecol 1981;58:609–613. [PubMed: 7301237]
8. Sibai BM. Eclampsia VI. Maternal-perinatal outcome in 254 cases. Am J Obstet Gynecol 1990;163:1049–1055. [PubMed: 2403130]
9. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, Smith D, The Magpie Trial Collaboration Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: A randomised placebo-controlled trial. Lancet 2002;359:1877–1890. [PubMed: 12057549]
10. Chien PFW, Khan KS, Arnott N. Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: An overview of the evidence from randomised trials. Br J Obstet Gynaecol 1996;103:1085–1091. [PubMed: 8916993]
11. Duley L, Henderson-Smart D. Magnesium sulphate versus phenytoin for eclampsia. Cochrane Database Syst Rev 2003:4.
12. Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. N Engl J Med 1995;333:201–205. [PubMed: 7791836]
13. Belfort MA, Anthony J, Saade GR, Allen JC Jr. the Nimodipine Study Group. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med 2003;348:304–311. [PubMed: 12540643]
14. Duley L, Henderson-Smart D. Magnesium sulphate versus diazepam for eclampsia. Cochrane Database Syst Rev 2003:4.
15. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the collaborative eclampsia trial. Lancet 1995;345:1455–1463. [PubMed: 7769899]
16. Gülmezoglu AM, Duley L. Use of anticonvulsants in eclampsia and pre-eclampsia: Survey of obstetricians in the United Kingdom and Republic of Ireland. BMJ 1998;316:975–976. [PubMed: 9550956]
17. Douglas KA, Redman CWG. Eclampsia in the United Kingdom. BMJ 1994;309:1395–1400. [PubMed: 7819845]
18. Donaldson JO. Does magnesium sulfate treat eclamptic convulsions? Clinical Neuropharmacology 1986;9:37–45. [PubMed: 3548953]
19. Taber EB, Tan L, Chao CR, Beall MH, Ross MG. Pharmacokinetics of ionized versus total magnesium in subjects with preterm labor and preeclampsia. Am J Obstet Gynecol 2002;186:1017–1021. [PubMed: 12015530]
20. Leveno, KJ.; Cunningham, FG. Management of preeclampsia. In: Lindheimer, MD.; Roberts, JM.; Cunningham, FG., editors. Chesley's Hypertensive Disorders in Pregnancy. Appleton & Lange; Stamford, CT: 1999. p. 543-580.

21. Sibai BM, Graham JM, McCubbin JH. A comparison of intravenous and intramuscular magnesium sulfate regimens in preeclampsia. Am J Obstet Gynecol 1984;150:728–733. [PubMed: 6496595]
22. Roberts, JM. Pregnancy-related hypertension. In: Creasy, RK.; Resnik, R.; Iams, JD., editors. Maternal-Fetal Medicine: Principles and Practice. Saunders; Philadelphia, PA: 2004. p. 884-887.
23. McCubbin JH, Sibai BM, Abdella TN, Anderson GD. Cardiopulmonary arrest due to acute maternal hypermagnesaemia. Lancet 1981;1:1058. [PubMed: 6112438]
24. Aali BS, Khazaeli P, Ghasemi F. Ionized and total magnesium concentration in patients with severe preeclampsia-eclampsia undergoing magnesium sulfate therapy. J Obstet Gynaecol Res 2007;33:138–143. [PubMed: 17441885]
25. Sibai BM, Spinnato JA, Watson DL, Lewis JA, Anderson GD. Effect of magnesium sulfate on electroencephalographic finding in preeclampsia-eclampsia. Obstet Gynecol 1984;64:261–266. [PubMed: 6738959]
26. Aali S, Khazaeli P, Ghasemi F, Mehdizadeh A. Serum magnesium and calcium ions in patients with severe pre-eclampsia/eclampsia undergoing magnesium sulfate therapy. Med Sci Monit 2007;13:CR191–CR194. [PubMed: 17392650]
27. Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, Nishio A. Mg^{2+} - Ca^{2+} interaction in contractility of vascular smooth muscle: Mg^{2+} versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. Can J Physiol Pharmacol 1987;65:729–745. [PubMed: 3300911]
28. Aloamaka CP, Ezimokhai M, Morrison J, Cherian T. Effect of pregnancy on relaxation of rat aorta to magnesium. Cardiovascular Research 1993;27:1629–1633. [PubMed: 8287441]
29. Longo M, Jain V, Vedernikov YP, Facchinetti F, Saade GR, Garfield RE. Endothelium dependence and gestational regulation of inhibition of vascular tone by magnesium sulfate in rat aorta. Am J Obstet Gynecol 2001;184:971–978. [PubMed: 11303207]
30. Euser AG, Cipolla MJ. Resistance artery vasodilation to magnesium sulfate during pregnancy and the postpartum state. Am J Physiol Heart Circ Physiol 2005;288:H1521–H1525. [PubMed: 15576433]
31. Nishio A, Gebrewold A, Altura BT, Altura BM. Comparative vasodilator effects of magnesium salts on rat mesenteric arterioles and venules. Arch Int Pharmacodyn 1989;298:139–163. [PubMed: 2757462]
32. Villamor E, Perez-Vizcaino F, Ruiz T, Tamargo J, Moro M. In vitro effects of magnesium sulfate in isolated intrapulmonary and mesenteric arteries of piglets. Pediatr Res 1996;39:1107–1112. [PubMed: 8725278]
33. Nelson SH, Suresh MS. Magnesium sulfate-induced relaxation of uterine arteries from pregnant and non-pregnant patients. Am J Obstet Gynecol 1991;164:1344–1350. [PubMed: 2035578]
34. Perales AJ, Torregrosa G, Salom JB, Miranda FJ, Alabadi JA, Monleon J, Alborch E. In vivo and in vitro effects of magnesium sulfate in the cerebrovascular bed of the goat. Am J Obstet Gynecol 1991;165:1534–1538. [PubMed: 1957890]
35. Belfort MA, Moise KJ Jr. Effect of magnesium sulfate on maternal brain blood flow in preeclampsia: A randomized, placebo-controlled study. Am J Obstet Gynecol 1992;167:661–666. [PubMed: 1530019]
36. Belfort MA, Saade GR, Moise KJ Jr. The effect of magnesium sulfate on maternal and fetal blood flow in pregnancy-induced hypertension. Acta Obstet Gynecol Scand 1993;72:526–530. [PubMed: 8213097]
37. Naidu S, Payne AJ, Moodley J, Hoffmann M, Gouws E. Randomised study assessing the effect of phenytoin and magnesium sulphate on maternal cerebral circulation in eclampsia using transcranial doppler ultrasound. Br J Obstet Gynaecol 1996;103:111–116. [PubMed: 8616125]
38. Schwartz RB, Feske SK, Polak JF, DeGirolami U, Iaia A, Beckner KM, Bravo SM, Klufas RA, Chai RY, Repke JT. Preeclampsia-eclampsia: Clinical and neuroradiographic correlates and insights into the pathogenesis of hypertensive encephalopathy. Radiology 2000;217:371–376. [PubMed: 11058630]
39. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, Pessin MS, Lamy C, Mas JL, Caplan LR. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494–500. [PubMed: 8559202]

40. Donaldson JO. Eclamptic hypertensive encephalopathy. Seminars in Neurology 1988;8:230–233. [PubMed: 3057555]
41. Hatab MR, Zeeman GG, Twickler DM. The effect of magnesium sulfate on large cerebral artery blood flow in severe preeclampsia. J Maternal-Fetal Neonat Med 2005;17:187–192.
42. Belfort MA, Saade GR, Yared M, Grunewald C, Herd JA, Varner MA, Nisell H. Change in estimated cerebral perfusion pressure after treatment with nimodipine or magnesium sulfate in patients with preeclampsia. Am J Obstet Gynecol 1999;181:402–407. [PubMed: 10454691]
43. Sherman R, Armory P, Moody P, Hope T, Mahajan RP. Effects of magnesium sulphate on cerebral haemodynamics in healthy volunteers: A transcranial doppler study. British Journal of Anaesthesia 2003;91:273–275. [PubMed: 12878627]
44. Scardo JA, Hogg BB, Newman RB. Favorable hemodynamic effects of manesium sulfate in preeclampsia. Am J Obstet Gynecol 1995;173:1249–1253. [PubMed: 7485331]
45. Standley CA, Batia L, Yueh G. Magnesium sulfate effectively reduces blood pressure in an animal model of preeclampsia. J Matern Fetal Neonatal Med 2006;19:171–176. [PubMed: 16690511]
46. Cipolla MJ, Vitullo L, McKinnon J. Cerebral artery reactivity changes during pregnancy and the postpartum period: A role in eclampsia? Am J Physiol Heart Circ Physiol 2004;286:H2127–H2132. [PubMed: 14751854]
47. Watson KV, Moldow CF, Ogburn PL, Jacob HS. Magnesium sulfate: Rationale for its use in preeclampsia. PNAS 1986;83:1075–1078. [PubMed: 3513161]
48. Ravn HB, Vissinger H, Kristensen SD, Wennmalm A, Thygesen K, Husted SE. Magnesium inhibits platelet activity - an infusion study in healthy volunteers. Thromb Haemostas 1996;75:939–944.
49. Goldkrand JW, Fuentes AM. The relation of angiotensin-converting enzyme to the pregnancy-induced hypertension-preeclampsia syndrome. Am J Obstet Gynecol 1986;154:792–800. [PubMed: 3008558]
50. Easton JD. Severe preeclampsia/eclampsia: Hypertensive encephalopathy of pregnancy? Cerebrovasc Dis 1998;8:53–58. [PubMed: 9645984]
51. Khan F, Belch JJF, MacLeod M, Mires G. Changes in endothelial function precede the clinical disease in women in whom preeclampsia develops. Hypertension 2005;46:1123–1128. [PubMed: 16230524]
52. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: An endothelial cell disorder. Am J Obstet Gynecol 1989;161:1200–1204. [PubMed: 2589440]
53. Fenstermacher J, Gross P, Sposito N, Acuff V, Pettersen S, Gruber K. Structural and functional variations in capillary systems within the brain. Ann N Y Acad Sci 1988;529:21–30. [PubMed: 3395069]
54. Reese TS, Karnovsky MJ. Fine structural localization of a blood-brain barrier to exogenous peroxidase. J Cell Biol 1967;34:207–217. [PubMed: 6033532]
55. Sedlakova R, Shivers RR, Del Maestro RF. Ultrastructure of the blood-brain barrier in the rabbit. J Submicrosc Cytol Pathol 1999;31:149–161. [PubMed: 10363362]
56. Brightman MW, Reese TS. Junctions between intimately apposed cell membranes in the vertebrate brain. J Cell Biol 1969;40:648–677. [PubMed: 5765759]
57. Kaplan, PW. Eclampsia. In: Kaplan, PW., editor. Neurologic Disease in Women. Demos Medical Publishing, Inc; New York, NY: 2006. p. 235-245.
58. Zunker P, Ley-Pozo J, Louwen F, Schuierer G, Holzgreve W, Ringelstein EB. Cerebral hemodynamics in pre-eclampsia/eclampsia syndrome. Ultrasound Obstet Gynecol 1995;6:411–415. [PubMed: 8903916]
59. Esen F, Erdem T, Aktan D, Kalayci R, Cakar N, Kaya M, Telci L. Effects of magnesium administration on brain edema and blood-brain barrier breakdown after experimental traumatic brain injury in rats. Journal of Neurosurgical Anesthesiology 2003;15:119–125. [PubMed: 12657997]
60. Esen F, Erdem T, Aktan D, Orhan M, Kaya M, Eraksoy H, Cakar N, Telci L. Effect of magnesium sulfate administration on blood-brain barrier in a rat model of intraperitoneal sepsis: A randomized controlled experimental study. Critical Care 2005;9:R18–R23. [PubMed: 15693962]
61. Kaya M, Kucuk M, Kalayci RB, Cimen V, Gurses C, Elmas I, Arican N. Magnesium sulfate attenuates increased blood-brain barrier permeability during insulin-induced hypoglycemia in rats. Can J Physiol Pharmacol 2001;79:793–798. [PubMed: 11599780]

62. Kaya M, Gulturk S, Elmas I, Arican N, Kocyildiz ZC, Kucuk M, Yorulmaz H, Sivas A. The effects of magnesium sulfate on blood-brain barrier disruption caused by intracarotid injection of hyperosmolar mannitol in rats. Life Sci 2004;76:201–212. [PubMed: 15519365]
63. Euser AG, Bullinger L, Cipolla MJ. Magnesium sulphate treatment decreases blood brain barrier permeability during acute hypertension in pregnant rats. Exp Physiol 2008;93:254–261. [PubMed: 17933863]
64. Feldman Z, Gurevitch B, Artru AA, Oppenheim A, Shohami E, Reichenthal E, Shapira Y. Effect of magnesium given 1 hour after head trauma on brain edema and neurological outcome. J Neurosurg 1996;85:131–137. [PubMed: 8683262]
65. Ghabriel MN, Thomas A, Vink R. Magnesium restores altered aquaporin-4 immunoreactivity following traumatic brain injury to a pre-injury state. Acta Neurochir Suppl 2006;96:402–406. [PubMed: 16671494]
66. Okiyama K, Smith DH, Gennarelli TA, Simon RP, Leach M, McIntosh TK. The sodium channel blocker and glutamate release inhibitor BW1003C87 and magnesium attenuate regional cerebral edema following experimental brain injury in the rat. J Neurochem 1995;64:802–809. [PubMed: 7830074]
67. Turkoglu OF, Eroglu H, Okutan O, Tun MK, Bodur E, Sargon MF, Öner L, Beskonakli E. A comparative study of treatment for brain edema: Magnesium sulphate versus dexamethasone sodium phosphate. J Clin Neurosci 2008;15:60–65. [PubMed: 18061457]
68. Fawcett WJ, Haxby EJ, Male DA. Magnesium: Physiology and pharmacology. British Journal of Anaesthesia 1999;83:302–320. [PubMed: 10618948]
69. Yuan SY. Signal transduction pathways in enhanced microvascular permeability. Microcirculation 2000;7:395–403. [PubMed: 11142336]
70. Yuan Y, Huang Q, Wu HM. Myosin light chain phosphorylation: Modulation of basal and agonist-stimulated venular permeability. Am J Physiol 1997:272.
71. Garcia JG, Davis HW, Patterson CE. Regulation of endothelial cell gap formation and barrier dysfunction: Role of myosin light chain phosphorylation. J Cell Physiol 1995;163:510–522. [PubMed: 7775594]
72. Mayhan WG, Heistad DD. Permeability of blood-brain barrier to various sized molecules. Am J Physiol Heart Circ Physiol 1985;248:H712–H718.
73. Kaplan PW, Lesser RP, Fisher RS, Repke JT, Hanley DF. No, magnesium sulfate should not be used in treating eclamptic seizures. Arch Neurol 1988;45:1361–1364. [PubMed: 3058097]
74. Ramanathan J, Sibai BM, Pillai R, Angel JJ. Neuromuscular transmission studies in preeclamptic women receiving magnesium sulfate. Am J Obstet Gynecol 1988;158:40–46. [PubMed: 2827486]
75. Somjen G, Hilmy M, Stephen CR. Failure to anesthetize human subjects by intravenous administration of magnesium sulfate. J Pharmac Exp Ther 1966;154:652–659.
76. Koontz WL, Reid KH. Effect of parenteral magnesium sulfate on penicillin-induced seizure foci in anesthetized cats. Am J Obstet Gynecol 1985;153:96–99. [PubMed: 4037007]
77. Goldman RS, Finkbeiner SM. Therapeutic use of magnesium sulfate in selected cases of cerebral ischemia and seizure. N Engl J Med 1988;319:1224–1225. [PubMed: 3173462]
78. Hallak M, Berman RF, Irtenkauf SM, Janusz C, Cotton DB. Magnesium sulfate treatment decreases N-methyl-d-aspartate receptor binding in the rat brain: An autoradiographic study. J Soc Gynecol Invest 1994;1:25–30.
79. Lipton SA, Rosenberg PA. Excitatory amino acids as a final common pathway for neurologic disorders. N Engl J Med 1994;330:613–620. [PubMed: 7905600]
80. Dingledine R, Hynes MA, King GL. Involvment of N-methyl-d-aspartate receptors in epileptiform bursting in the rat hippocampal slice. J Physiol 1986;380:175–189. [PubMed: 2886653]
81. Hallak M, Berman RF, Irtenkauf SM, Evans MI, Cotton DB. Peripheral magnesium sulfate enters the brain and increases the threshold for hippocampal seizures in rats. Am J Obstet Gynecol 1992;167:1605–1610. [PubMed: 1471674]
82. Cotton DB, Hallak M, Janusz C, Irtenkauf SM, Berman RF. Central anticonvulsant effects of magnesium sulfate on N-methyl-d-aspartate-induced seizures. Am J Obstet Gynecol 1993;198:974–978. [PubMed: 8456911]

83. Borges LF, Gucer G. Effect of magnesium on epileptic foci. Epilepsia 1978;19:81–91. [PubMed: 414910]
84. Thurnau GR, Kemp DB, Jarvis A. Cerebrospinal fluid levels of magnesium in patients with preeclampsia after treatment with intravenous magnesium sulfate: A preliminary report. Am J Obstet Gynecol 1987;157:1435–1438. [PubMed: 3425649]
85. Hilmy MI, Somjen GG. Distribution and tissue uptake of magnesium related to its pharmacological effects. Am J Physiol 1968;214:406–413. [PubMed: 5639567]
86. Kato G, Somjen GG. Effects of micro-iontophoretic administration of magnesium and calcium on neurones in the central nervous system of cats. J Neurobiol 1969;1:181–195. [PubMed: 4334646]
87. Amiry-Moghaddam M, Otsuka T, Hurn PD, Traystman RJ, Haug FM, Froehner SC, Adams ME, Neely JD, Agre P, Ottersen OP, Bhardwaj A. An alpha-syntrophin-dependent pool of AQP4 in astroglial end-feet confers bidirectional water flow between blood and brain. PNAS 2003;100:2106–2111. [PubMed: 12578959]
88. Nielsen S, Nagelhus EA, Amiry-Moghaddam M, Bourque C, Agre P, Ottersen OP. Specialized membrane domains for water transport in glial cells: High-resolution immunogold cytochemistry of aquaporin-4 in rat brain. J Neurosci 1997;17:171–180. [PubMed: 8987746]
89. Amiry-Moghaddam M, Xue R, Haug FM, Neely JD, Bhardwaj A, Agre P, Adams ME, Froehner SC, Mori S, Ottersen OP. Alpha-syntrophin deletion removes the perivascular but not endothelial pool of aquaporin-4 at the blood-brain barrier and delays the development of brain edema in an experimental model of acute hyponatremia. FASEB J 2004;18:542–544. [PubMed: 14734638]
90. Papadopoulos MC, Verkman AS. Aquaporin-4 gene disruption in mice reduces brain swelling and mortality in pneumococcal meningitis. J Biol Chem 2005;280:13906–13912. [PubMed: 15695511]
91. Taniguchi M, Yamashita T, Kumura E, Tamatani M, Kobayashi A, Yokawa T, Maruno M, Kato A, Ohnishi T, Kohmura E, Tohyama M, Yoshimine T. Induction of aquaporin-4 water channel mRNA after focal cerebral ischemia in rat. Molecular Brain Research 2000;78:131–137. [PubMed: 10891592]
92. Quick AM, Cipolla MJ. Pregnancy-induced up-regulation of aquaporin-4 protein in brain and its role in eclampsia. FASEB J 2005;19:170–175. [PubMed: 15677340]
93. Podjarny E, Losonczy G, Baylis C. Animal models of preeclampsia. Semin Perinat 2004;24:596–606.
94. Euser AG, Cipolla MJ. Cerebral blood flow autoregulation and edema formation during pregnancy in anesthetized rats. Hypertension 2007;49:334–340. [PubMed: 17200432]
95. Cipolla MJ. Cerebrovascular function in pregnancy and eclampsia. Hypertension 2007;50:14–24. [PubMed: 17548723]

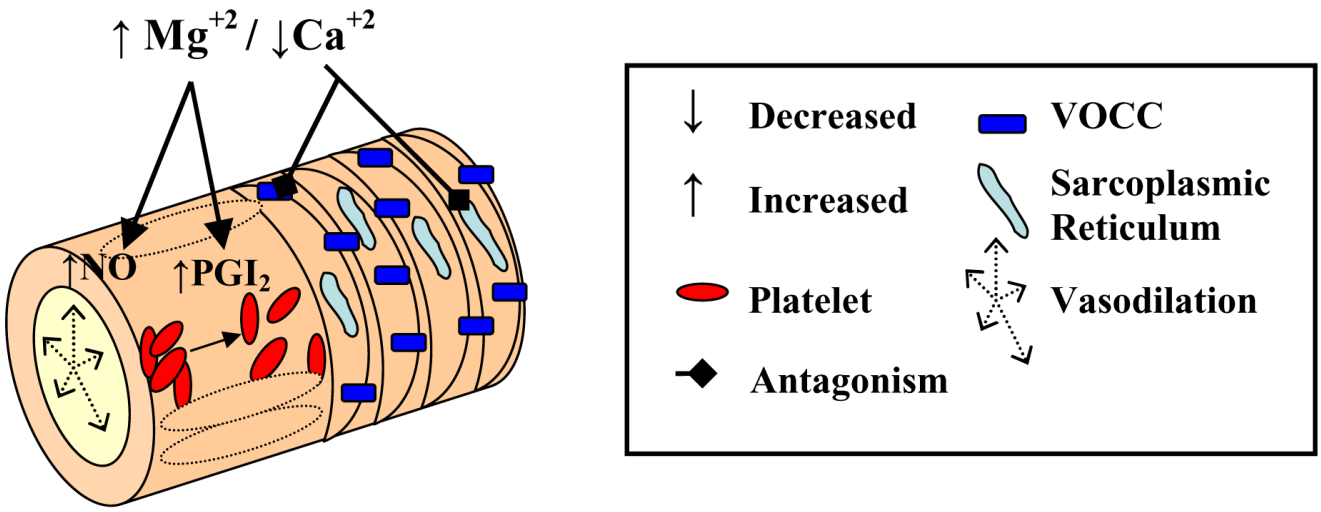

Figure 1. Vascular Effects of Magnesium Sulfate

Magnesium is a potent vasodilator of uterine and mesenteric arteries, and aorta, but has minimal effect on cerebral arteries. In vascular smooth muscle, magnesium competes with calcium for binding sites, in this case for voltage-operated calcium channels (VOCC). Decreased calcium channel activity lowers intracellular calcium, causing relaxation and vasodilation. In endothelium, magnesium has been shown to increase production of prostaglandin I_2 (through unknown mechanisms), which in turn decreases platelet aggregation. Magnesium also increases NO production causing vasodilation.

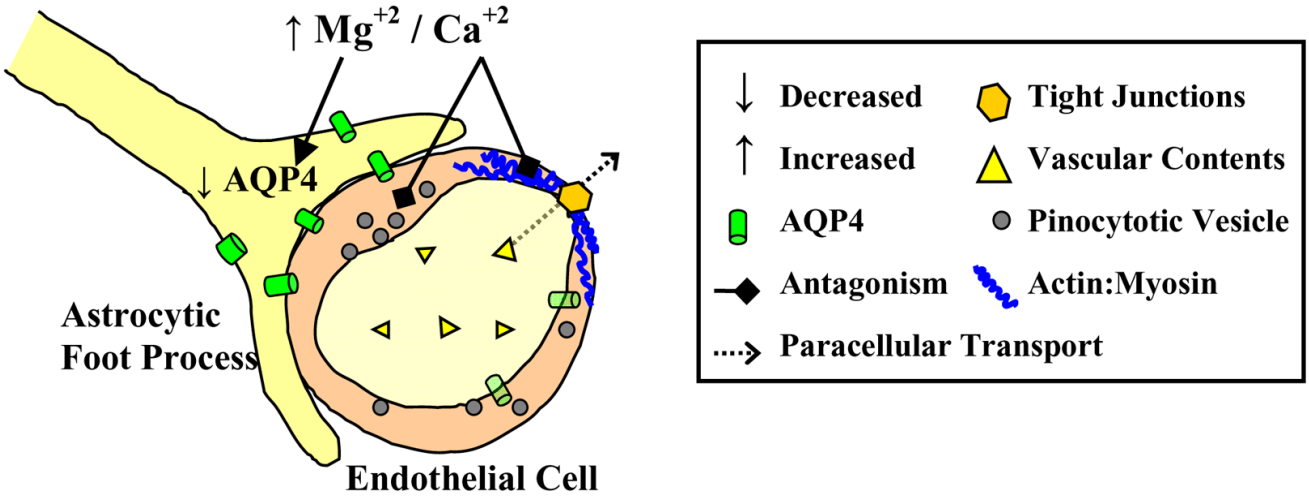

Figure 2. Effect of Magnesium Sulfate on Cerebral Edema and the Blood-brain Barrier

The calcium antagonistic effects of magnesium can also affect the cerebral endothelium that forms the blood-brain barrier. Decreased cell calcium inhibits endothelial contraction and opening of tight junctions that are linked to the actin cytoskeleton. Decreased tight junction permeability limits paracellular transport of vascular contents, ions and proteins, which can promote vasogenic edema and seizures. It is also possible that magnesium sulfate diminishes transcellular transport by limiting pinocytosis that is known to occur rapidly during acute hypertension. Magnesium may also downregulate aquaporin 4 (AQP4), a water channel protein localized to astrocytic endfeet, and possibly cerebral endothelium, that is associated with cerebral edema formation (through unknown mechanisms).

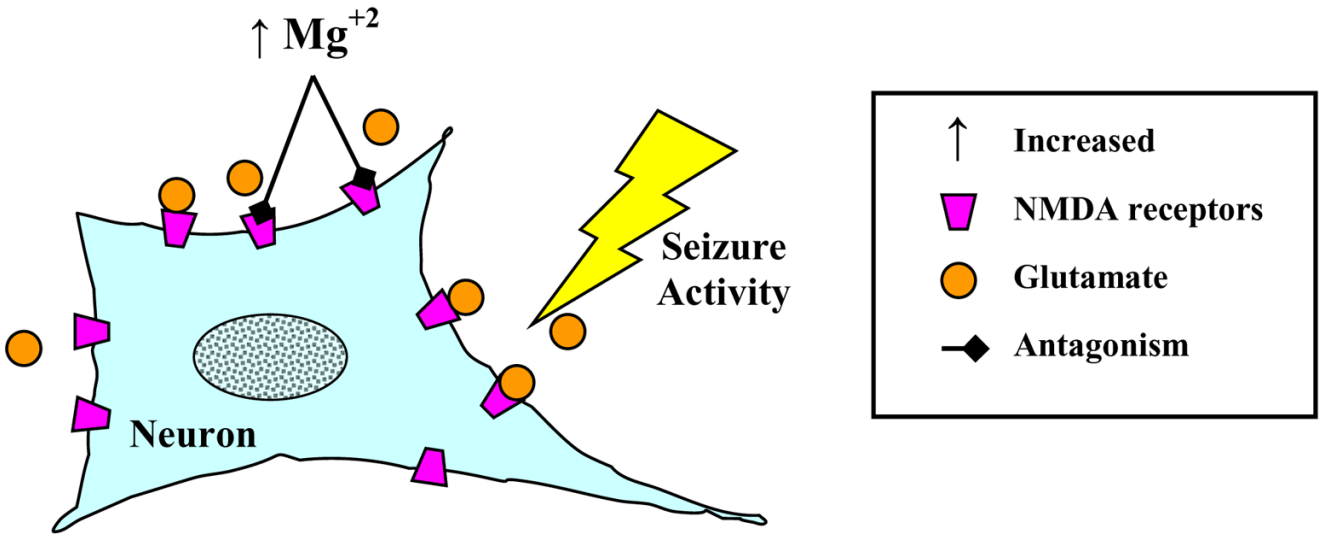

Figure 3. Anticonvulsant Activity of Magnesium Sulfate

Seizures consist of an excessive release of excitotoxic neurotransmitters including glutamate. Excessive glutamate can activate the N-methyl-D-aspartate (NMDA) receptor, leading to massive depolarization of neuronal networks and bursts of action potentials. Magnesium may act to increase the seizure threshold by inhibiting NMDA receptors, thereby limiting the effect of glutamate.

Table 1

Vascular Effects of Magnesium Sulfate.

Cellular Target	Mode of Action	Possible Mechanism(s)
Smooth Muscle Uterine +++ Mesenteric +++ Aorta +++ Cerebral +	Relaxation ↓ Vasodilation ↓ Decreased Vascular Resistance	Calcium Antagonism Decreased Voltage-operated Calcium Channel (VOCC) Activity Decreased $[Ca^{+2}]_i$ Release From Sarcoplasmic Reticulum
Endothelium	Decreased Platelet Aggregation	Increased Prostaglandin I_2 (PGI_2)
	Vasodilation	Increased Nitric Oxide (NO, Gestation Dependent)

Table 2

Effect of Magnesium Sulfate on Cerebral Edema and the Blood-brain Barrier.

Cellular Target	Mode of Action	Possible Mechanism
Cerebral Endothelium	Decreased Blood-brain Barrier (BBB) disruption ↓ Limited Cerebral Edema Formation Via Paracellular Transport	Calcium Antagonism ↓ Decreased Cell Contraction ↓ Decreased Tight Junction Permeability
	Limited Transcellular Transport	Decreased Pinocytosis
Astrocyte	Limited Cerebral Edema	Decreased Aquaporin 4 (AQP4) Expression

Table 3

Anticonvulsant Activity of Magnesium Sulfate.

Cellular Target	Mode of Action	Possible Mechanism
Neurons	Increased Seizure Threshold	N-Methyl-D-Aspartate (NMDA) Receptor Antagonism ↓ Decreased Effect of Glutamate, Limiting Massive Neuronal Depolarization