Magnesium in acute and chronic brain injury: an update

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> Abstract. While brain free magnesium levels have been shown to decline in a number of acute and chronic brain pathologies, the mechanisms of such decline and the potential for magnesium administration as a therapeutic intervention are still unclear. In acute brain injury, magnesium therapy has failed in recent clinical trials of trauma, presumably because of an intact blood brain barrier at the time of administration reducing central penetration. Under such conditions, magnesium's peripheral effects on cardiovascular parameters may dominate over the central, and potentially neuroprotective, effects of the compound. In contrast, magnesium has been demonstrated to be beneficial in lacunar strokes, albeit that recent animal studies indicate that this effect is without any significant reduction of lesion size. Postnatal magnesium has also been shown to improve neurological outcome in term neonates with perinatal asphyxia, although this may be limited to cases of mild to moderate brain injury; no effect is observed following severe brain injury. Prenatal magnesium has been reported to be beneficial for outcome in very preterm infants, although this may only be at low doses. Combination therapies are also showing promise in experimental studies, with combined magnesium and mild hypothermia as well as magnesium and polyethylene glycol proving effective in ischemic stroke and in spinal cord injury, respectively. With respect to chronic brain injury, recent results indicate that magnesium deficient mice are susceptible to developing Parkinson's disease, which is consistent with earlier findings that magnesium deficiency over a number of generations is associated with the development of Parkinson's disease. The latter was associated with the appearance of variants of the TRPM channels. Our recent studies have shown that Parkinson's disease is associated with reduced TRPM2 and TRPM7 channel mRNA expression. Taken together, a more complete picture is emerging of the role of magnesium in brain injury, its therapeutic potential as well the mechanisms associated with its decline.

Key words: magnesium, neurotrauma, ischemia, hypoxia, neurodegeneration, Parkinson's disease

Brain magnesium levels have now been shown to decline in a number of acute and chronic pathologies of the brain including traumatic brain injury [1], migraine [2], cocaine exposure [3], ethanol intoxication [4, 5], stroke [6] and subarachnoid hemorrhage [7], with mounting evidence supporting similar declines in depression and neurodegeneration [8-11]. Accordingly, there has been a considerable research effort directed toward establishing the mechanisms of such decline and the potential for magnesium administration as a therapeutic intervention. While a number of excellent reviews have

previously summarized progress in this field of magnesium research [12-14], few have covered a spectrum of acute and chronic brain pathologies. The current review therefore highlights recent progress in brain magnesium research focusing on advances of relevance to various pathologies.

Traumatic brain injury

Despite the considerable pre-clinical evidence from rodent models that magnesium therapy improves outcome after traumatic brain injury [12], magnesium therapy has failed in a recent clinical trial of trauma [15]. Although the standard care in the clinical trial was to correct plasma magnesium concentration in all patients, those in the magnesium treatment group received additional magnesium to at least double plasma magnesium concentration. At this concentration, magnesium did not deliver any improvement in outcome and actually was deleterious with respect to placebo on a number of markers. While reflecting the general dose-response characteristics previously described for magnesium administration in the pre-clinical studies [16], attention has nonetheless been drawn to the fact that in human TBI, intravenous magnesium administration only marginally increases CSF magnesium concentration [17]. Whether this small increase in CSF concentration is sufficient to increase brain cellular free magnesium concentration is critical given that the increase in brain free magnesium concentration is essential to confer neuroprotection [16]. Entry of magnesium into the CNS is dependent on the integrity of the blood brain barrier. While animal models of trauma produce extensive opening of the blood brain barrier that facilitates magnesium entry into the CNS for at least 24 h [18, 19], such an opening is not always present in human trauma [20]. Therefore magnesium may not have entered as it did in the pre-clinical studies and, under these circumstances, peripheral effects of magnesium administration may dominate over central effects, which in brain injury would be deleterious to critical parameters such as blood pressure and cerebral perfusion. A better understanding of magnesium entry into the human CNS is required to overcome this barrier to therapy.

Stroke

Magnesium therapy has also been described in the clinical stroke literature [21], with similar negative results as in the trauma trial. However, unlike the trauma trial, magnesium was shown to be beneficial in a subgroup of patients with noncortical, or lacunar strokes. It is well known that the blood brain barrier around infarcted tissue is highly permeable, thus potentially facilitating local magnesium entry to the injured tissue. Subsequent analysis of the original trial data indicated that the beneficial effects of magnesium on lacunar strokes could not be attributed to other baseline factors such as severity of stroke, blood pressure or time to treatment [22], although there was a strong correlation with age of patient. The authors were unable to rule out that the positive findings may have been influenced by such other confounding factors and have therefore recommended that a large clinical trial of magnesium in lacunar clinical syndromes be conducted.

Of interest has been the subsequent pre-clinical study examining the effects of magnesium on lacunar strokes. Despite reducing blood pressure and improving motor outcome, magnesium did not significantly reduce infarct size [23], which is contrary to expectations that infarct size correlates with neurological outcome. Whether this indicates that infarct size is not as important as synaptic connectivity is yet to be determined.

Neonatal brain injury

A number of studies have suggested that maternal magnesium administration may be of benefit to pediatric outcome, although this view is not universally held [24]. A recent meta-analysis of all trials has nonetheless recommended the use of magnesium for neuroprotection in the preterm fetus [25]. These studies have clearly shown that low-dose prenatal magnesium is beneficial for outcome in very preterm infants and that its administration does not increase mortality. The dose is particularly significant given that high prenatal doses of magnesium have been shown to be deleterious to neonatal outcome [24]. While the reasons for this dose effect are unclear, administration of high doses of magnesium have been purported to be detrimental to the fetal brain in critical periods of neurodevelopment, in part by inducing apoptotic cell death [26].

Beneficial effects of magnesium administration are not limited to the prenatal period with recent studies demonstrating that postnatal magnesium administration also improves neurological outcome in term neonates with perinatal asphyxia at discharge [27] as well as at 18 months [28]. Preclinical studies suggest that these results should be interpreted with caution given that the protective effects of magnesium in animals have only been observed in mild to moderate brain injury, with no positive effects observed following severe brain injury [29].

Combination treatment in acute injury

A number of reports have supported combination therapy with magnesium, which is unsurprising given that brain injury is widely considered to be the result of multiple injury factors that combine to culminate in neuronal cell death. Targeting an individual injury factor is therefore unlikely to result in a beneficial outcome, and multipotential therapies that target more than one injury factor are gaining increasing attention [30]. To date, various combinations with magnesium have been examined in stroke and traumatic CNS injury including magnesium with glutamate antagonists [31], growth factors [32], B vitamins [33], antioxidants [34, 35], immunosuppressants [36] or hypothermia [34, 37]. The studies have produced mixed results in preclinical studies, although the combination of magnesium and hypothermia has produced promising results. Clinical trials examining the efficacy of combined hypothermia and magnesium have been recommended for stroke.

Neurodegeneration

With respect to chronic brain injury and neurodegeneration, a critical role for magnesium has been implicated in Alzheimer's disease [8], Huntington's disease [11], mitochondrial cytopathies [38] and depression [10], although most recent studies have focused on Parkinson's disease. These recent reports have shown that magnesium deficient mice are susceptible to developing Parkinson's disease [39], and that magnesium administration is beneficial in an in vitro model of Parkinson's disease [40]. In effect, they describe that magnesium concentration is critical in disease onset, which is consistent with the earlier finding that magnesium deficiency over a number of generations is associated with the development of Parkinson's disease [41]. While the exact mechanisms by which magnesium is associated with Parkinson's disease are unknown, the appearance of variants of the TRPM channels [42] that are linked with magnesium transport suggest that magnesium transporters may play a role in disease onset under some circumstances. This hypothesis is supported by our own studies (unpublished results) that have shown that Parkinson's disease is associated with reduced TRPM2 and TRPM7 channel mRNA expression. Whether this reduced magnesium transport initiates the inflammation and oxidative stress that have been widely reported in Parkinson's disease is yet to be investigated. Aside from disease onset, magnesium has also been shown to reduce dyskinesia (abnormal motor movements) in Parkinson's disease [43], suggesting some interaction between neurotransmitter release and magnesium levels.

Conclusion

Magnesium continues to be of interest to those who study acute and chronic brain injury. Clear associations have now been described between magnesium homeostasis and functional outcome in acute injury, as well as in disease onset and progression in chronic injury and neurodegeneration. However, it is also apparent that just administering magnesium as a therapeutic intervention is a simplistic approach that does not always achieve desired outcomes. Several barriers exist to successful therapeutic intervention, not the least being that experimental models of CNS disease and injury do not always fully replicate the human condition. The role and characterization of magnesium transporters is also becoming increasingly important, particularly in neurodegeneration. While significant progress has been made in understanding the role of magnesium in these various brain pathologies, its therapeutic potential as well the mechanisms associated with its decline, there is still much to be done to fully capitalize the potential of this important ion.

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References

- Vink R, McIntosh TK, Demediuk P, Weiner MW, Faden AI. Decline in intracellular free magnesium concentration is associated with irreversible tissue injury following brain trauma. *J Biol Chem* 1988; 263: 757-61.
- Ramadan NM, Halvorson H, Vande-Linde A, Levine SR, Helpern JA, Welch KMA. Low brain magnesium in migraine. *Headache* 1989; 29: 416-9.
- Altura BM, Gupta RK. Cocaine induces intracellular free Mg deficits, ischemia and stroke as observed by in-vivo ³¹P NMR of the brain. *Biochim Biophys Acta* 1992; 1111: 271-4.
- Altura BM. Ethanol promotes rapid depletion of intracellular free Mg in cerebral vascular smooth muscle cells - possible relation to alcohol induced behavioural and stroke like effects. *Alcohol* 1993; 10: 563-6.
- Mullins PGM, Vink R. Chronic alcohol exposure decreases brain intracellular free magnesium concentration in rats. *Neuroreport* 1995; 6: 1633-6.
- Lin MC, Huang YL, Liu HW, Yang DY, Lee CP, Yang LL, et al. On-line microdialysis-graphite furnace atomic absorption spectrometry in the determination of brain magnesium levels in gerbils subjected to cerebral ischemia/reperfusion. J Am Coll Nutr 2004; 23: 5618-565S.

- Yang H, Tang X, Tan L, Zeng L, Hu Z. Use of ³¹P magnetic resonance spectroscopy to study the effect of cortical magnesium and energy metabolism after subarachnoid hemorrhage. *Cerebrovasc Dis* 2008; 26: 223-30.
- Andrasi E, Igaz S, Molnar Z, Mako S. Disturbances of magnesium concentrations in various brain areas in Alzheimer's disease. *Magnes Res* 2000; 13: 189-96.
- Nechifor M. Interactions between magnesium and psychotropic drugs. *Magnes Res* 2008; 21: 97-100.
- Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I, Mykletun A. Association between magnesium intake and depression and anxiety in community-dwelling adults: the Hordaland Health Study. *Aust N Z J Psychiatry* 2009; 43: 45-52.
- 11. Starling AJ, Andre VM, Cepeda C, de Lima M, Chandler SH, Levine MS. Alterations in N-methyl-D-aspartate receptor sensitivity and magnesium blockade occur early in development in the R6/2 mouse model of Huntington's disease. J Neurosci Res 2005; 82: 377-86.
- Vink R, Cernak I. Regulation of brain intracellular free magnesium following traumatic injury to the central nervous system. *Front Biosci* 2000; 5: 656-65.
- Ozgurtas T, Kahraman S. State of the art of new data on the role of magnesium in brain injury: clinical interest of measurements of total and ionized magnesium. *Magnes Res* 2004; 17: 327-34.
- Romani AM. Magnesium homeostasis and alcohol consumption. *Magnes Res* 2008; 21: 197-204.
- Temkin NR, Anderson GD, Winn HR, et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial. *Lancet Neurol* 2007; 6: 29-38.
- Heath DL, Vink R. Optimization of magnesium therapy following severe diffuse axonal brain injury in rats. *J Pharmacol Exp Ther* 1999; 288: 1311-6.
- 17. McKee JA, Brewer RP, Macy GE, Phillips-Bute B, Campbell KA, Borel CO, et al. Analysis of the brain bioavailability of peripherally administered magnesium sulfate: A study in humans with acute brain injury undergoing prolonged induced hypermagnesemia. *Crit Care Med* 2005; 33: 661-6.
- Habgood MD, Bye N, Dziegielewska KM, Ek CJ, Lane MA, Potter A, *et al.* Changes in blood-brain barrier permeability to large and small molecules following traumatic brain injury in mice. *Eur J Neurosci* 2007; 25: 231-8.
- Heath DL, Vink R. Delayed therapy with magnesium up to 24 h following traumatic brain injury improves motor outcome. *J Neurosurg* 1999; 90: 504-9.
- Miller JW, D'Ambrosio R. When basic research doesn't translate to the bedside-lessons from the Magnesium Brain Trauma study. *Epilepsy Curr* 2007; 7: 133-5.
- Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. *Lancet* 2004; 363: 439-45.

- Aslanyan S, Weir CJ, Muir KW, Lees KR. Magnesium for treatment of acute lacunar stroke syndromes: further analysis of the IMAGES trial. *Stroke* 2007; 38: 1269-73.
- Lecrux C, McCabe C, Weir CJ, Gallagher L, Mullin J, Touzani O, *et al.* Effects of magnesium treatment in a model of internal capsule lesion in spontaneously hypertensive rats. *Stroke* 2008; 39: 448-54.
- Mittendorf R, Dammann O, Lee KS. Brain lesions in newborns exposed to high-dose magnesium sulfate during preterm labor. *J Perinatol* 2006; 26: 57-63.
- 25. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* 2009: CD004661.
- 26. Dribben WH, Creeley CE, Wang HH, Smith DJ, Farber NB, Olney JW. High dose magnesium sulfate exposure induces apoptotic cell death in the developing neonatal mouse brain. *Neonatology* 2009; 96: 23-32.
- 27. Bhat MA, Charoo BA, Bhat JI, Ahmad SM, Ali SW, Mufti MU. Magnesium sulfate in severe perinatal asphyxia: a randomized, placebo-controlled trial. *Pediatrics* 2009; 123: e764-9.
- 28. Ichiba H, Yokoi T, Tamai H, Ueda T, Kim TJ, Yamano T. Neurodevelopmental outcome of infants with birth asphyxia treated with magnesium sulfate. *Pediatr Int* 2006; 48: 70-5.
- 29. Spandou E, Soubasi V, Papoutsopoulou S, Augoustides-Savvopoulou P, Loizidis T, Pazaiti A, et al. Neuroprotective effect of long-term MgSO₄ administration after cerebral hypoxia-ischemia in newborn rats is related to the severity of brain damage. *Reprod Sci* 2007; 14: 667-77.
- Vink R, Nimmo AJ. Multifunctional drugs for head injury. *Neurotherapeutics* 2009; 6: 28-42.
- 31. Imer M, Omay B, Uzunkol A, Erdem T, Sabanci P, Karasu A, et al. Effect of magnesium, MK-801 and combination of magnesium and MK-801 on blood-brain barrier permeability and brain edema after experimental traumatic diffuse brain injury. *Neurol Res* 2009; 11: 11.
- 32. Guluma KZ, Saatman KE, Brown A, Raghupathi R, McIntosh TK. Sequential pharmacotherapy with magnesium chloride and basic fibroblast growth factor after fluid percussion brain injury results in less neuromotor efficacy than that achieved with magnesium alone. J Neurotrauma 1999; 16: 311-2.
- Barbre AB, Hoane MR. Magnesium and riboflavin combination therapy following cortical contusion injury in the rat. *Brain Res Bull* 2006; 69: 639-46.
- 34. Scholler K, Zausinger S, Baethmann A, Schmid-Elsaesser R. Neuroprotection in ischemic strokecombination drug therapy and mild hypothermia in a rat model of permanent focal cerebral ischemia. *Brain Res* 2004; 1023: 272-8.

- 35. Kwon BK, Roy J, Lee JH, Okon EB, Zhang H, Marx JC, et al. Magnesium chloride in a polyethylene glycol formulation as a neuroprotective therapy for acute spinal cord injury: preclinical refinement and optimization. J Neurotrauma 2009; 24: 24.
- 36. Chung SY, Lin JY, Lin MC, Liu HM, Wang MF, Cheng FC. Synergistic efficacy of magnesium sulfate and FK506 on cerebral ischemia-induced infarct volume in gerbil. *Med Sci Monit* 2004; 10: BR105-BR108.
- 37. Meloni BP, Campbell K, Zhu H, Knuckey NW. In search of clinical neuroprotection after brain ischemia: the case for mild hypothermia (35°C) and magnesium. *Stroke* 2009; 40: 2236-40.
- Iotti S, Malucelli E. In vivo assessment of Mg²⁺ in human brain and skeletal muscle by ³¹P-MRS. *Magnes Res* 2008; 21: 157-62.
- 39. Muroyama A, Inaka M, Matsushima H, Sugino H, Marunaka Y, Mitsumoto Y. Enhanced susceptibility to MPTP neurotoxicity in magnesium-deficient C57BL/6N mice. *Neurosci Res* 2009; 63: 72-5.

- 40. Hashimoto T, Nishi K, Nagasao J, Tsuji S, Oyanagi K. Magnesium exerts both preventive and ameliorating effects in an in vitro rat Parkinson disease model involving 1-methyl-4-phenylpyridinium (MPP+) toxicity in dopaminergic neurons. *Brain Res* 2008; 1197: 143-51.
- 41. Oyanagi K, Kawakami E, Kikuchi-Horie K, *et al.* Magnesium deficiency over generations in rats with special references to the pathogenesis of the Parkinsonismdementia complex and amyotrophic lateral sclerosis of Guam. *Neuropathology* 2006; 26: 115-28.
- Hermosura MC, Garruto RM. TRPM7 and TRPM2-Candidate susceptibility genes for Western Pacific ALS and PD? *Biochim Biophys Acta* 2007; 1772: 822-35.
- Chassain C, Eschalier A, Durif F. Antidyskinetic effect of magnesium sulfate in MPTP-lesioned monkeys. *Exp Neurol* 2003; 182: 490-6.