Effect of Profound Hypermagnesemia on Spinal Cord Glucose Utilization in Rats

Michele D. Szabo, MD, and Gregory Crosby, MD

The purpose of our study was to investigate the effect of hypermagnesemia on spinal metabolic rate. The 2-[\(^{14}\)C]deoxyglucose technique was used to measure regional glucose utilization in the lumbar spinal cord of paralyzed, mechanically ventilated rats receiving 70% nitrous oxide and an intravenous infusion of either saline (n = 5) or magnesium sulfate (n = 5). Plasma magnesium concentrations were 6.75 ±0.5 and 0.9 ±0.5 mM (p <0.01) in hypermagnesemic and control rats, respectively. Hypermagnesemic rats were hypotensive (88 ±1 vs. 130 ±4 mm Hg, p <0.01) but blood pressure remained within the autoregulatory range. Glucose utilization was reduced 26–45% in spinal gray matter and 53–63% in spinal white matter during hypermagnesemia. We conclude that magnesium is a potent spinal metabolic depressant and that this action, which is unusually prominent in spinal white matter, is a plausible explanation for the recently reported beneficial effect of magnesium therapy during spinal cord ischemia. (Stroke 1988;19:747–749)

Recent work indicates that the spinal cord’s ability to tolerate an ischemic insult is improved by prior treatment with magnesium, and it has been suggested that spinal metabolic depression may partially contribute to this beneficial effect.1,2 It is not clear that magnesium reduces central nervous system (CNS) metabolism in vivo, however, even though it inhibits glycolysis3 and blocks neurotransmitter release in vitro.4 That is, magnesium crosses the blood–brain (spinal cord) barrier poorly,5 and increases in plasma magnesium concentration do not produce comparable changes in brain6 or cerebrospinal fluid7 magnesium concentrations. Indeed, the fact that profound hypermagnesemia does not substantially alter level of consciousness8 has been taken as evidence that magnesium is not a major CNS depressant. Accordingly, to determine whether metabolic depression is a plausible explanation for magnesium’s beneficial effect during spinal ischemia, we investigated the effect of hypermagnesemia on the spinal metabolic rate for glucose in normal rats.

Materials and Methods

The 2-[\(^{14}\)C]deoxyglucose (2-[\(^{14}\)C]DG) technique9 was used to measure glucose utilization in the lumbar spinal cord of 10 male Sprague-Dawley rats. A tracheostomy was performed, and bilateral femoral arterial and venous catheters were inserted during approximately 30 minutes of anesthesia with 1% halothane and 70% nitrous oxide. When surgery was complete, halothane was discontinued. The rats were paralyzed with 4 mg i.v. gallamine, supplemented as necessary, and ventilated mechanically. Five rats received an intravenous infusion of 50% magnesium sulfate solution over 75 minutes. Preliminary experiments established that profound arterial hypotension occurred occasionally with a fixed magnesium infusion rate. Therefore, the magnesium infusion was adjusted periodically to maintain mean arterial blood pressure (MABP) at > 80 mm Hg. The total dose of magnesium sulfate administered was approximately 400 mg in 0.8 ml of solution. Five control rats received a similar volume of saline intravenously over the same period. MABP, arterial blood gases, and arterial pH were measured in all rats. Rectal temperature was measured and maintained with a heat lamp.

Experiments were begun >1 hour after discontinuation of halothane and 30 minutes after the magnesium infusion was started by a bolus injection of 125 μCi/kg of 2-[\(^{14}\)C]DG. Timed arterial blood samples were taken during the 45-minute experiment for measurement of plasma glucose and 2-[\(^{14}\)C]DG concentrations. The magnesium infusion was continued throughout the experiment, and arterial blood was sampled for determination of plasma magnesium concentrations. The rats were killed with intravenous pentobarbital and saturated potassium chloride, and the lumbar spinal cord was removed quickly and processed for autoradiography as described.9 Sections 20 μm thick were cut at -20°C in a cryostat and autoradiographed along with a set of [\(^{14}\)C]methyl methacrylate standards. The autoradiographs generated by this procedure were analyzed with the aid of a computerized image-processing system.10 Optical density measurements were made bilaterally in a minimum of six autoradiographic sections. Local spinal glucose utilization was calculated from the tissue 14C concentrations, the time course of plasma glucose and 2-[\(^{14}\)C]DG concentrations, and the rate and lumped constants of normal rat brain according to the operational equation of the method.1 Data were analyzed with an unpaired t test.

Results

Plasma magnesium concentrations were 6.75 ±0.5 and 0.9 ±0.5 mM (13.5 ±1 and 1.8 ±1 meq/l)
(p<0.01) in hypermagnesemic and control rats, respectively. Apart from hypotension, hypermagnesemia produced no significant changes in the physiologic variables (Table 1). Moreover, since MABP remained within the range of autoregulation of spinal blood flow,11 it is unlikely that hypotension affected the results.

Hypermagnesemia reduced metabolism in all regions of spinal cord examined (Table 2). Glucose utilization was 26–45% lower than control in spinal gray matter; laminae I–III were affected least and utilization in lamina VII was decreased most. The changes in spinal white matter were even more profound. Hypermagnesemia was associated with a 53–63% decrease in glucose utilization by spinal white matter (Table 2).

Discussion

There have been conflicting opinions regarding the CNS effects of magnesium. Somjen et al11 first demonstrated that hypermagnesemia (plasma concentration 7.5 mM) does not produce anesthesia in humans and concluded that magnesium's divalent, cationic structure limits its ability to cross the blood–brain barrier. Moreover, although the success of magnesium for treating or preventing seizures in patients with toxemia of pregnancy suggests that magnesium enters the CNS in a therapeutic amount,5 such therapy does not reduce cerebral metabolic rate in toxemic patients.12 In contrast, we found that hypermagnesemia substantially reduced the metabolic rate of neural tissue. In fact, the magnitude of spinal metabolic depression we observed in vivo is consistent with in vitro work showing a 68% decrease in 2-[14C]DG uptake in retina exposed to media containing 15 mM magnesium.13 Elevating the plasma magnesium concentration to as much as 4 mM does not produce correspondingly large increases in cerebrospinal fluid magnesium,2 but brain and spinal cord magnesium concentrations increase somewhat when the plasma concentration approaches 10 mM.6 Thus, we presume that the high plasma concentration achieved in our study facilitated penetration of magnesium into the spinal cord and that the resulting tissue magnesium concentration was sufficient to profoundly reduce spinal metabolic rate. Indeed, since high magnesium concentrations are probably desirable when neural protection is the object of therapy, it is fortuitous

that such concentrations are consistent with reasonable cardiovascular stability.3 For example, despite high plasma magnesium concentrations, MABP remained within autoregulatory limits11 (Table 1); therefore, hypotension probably did not contribute to spinal metabolic depression. This is likely to be true even if autoregulation is altered by magnesium since the spinal metabolic effect of halothane, a general anesthetic that impairs autoregulation, is unaffected by hypotension of this magnitude.14

The mechanisms by which magnesium reduces spinal metabolism presumably include effects on synaptic transmission and glycolysis. Magnesium reduces synaptic transmission by competing with ionic calcium4–5 and inhibits glycolysis directly by inhibiting the enzyme phosphofructokinase.3 Both actions of magnesium probably explain the decreased rate of glucose utilization in spinal gray matter but (assuming uniform tissue distribution of magnesium) cannot explain fully the disproportionately larger effect of magnesium on spinal white matter metabolism. White matter typically has a lower rate of metabolism15,16 than gray matter (presumably because oligodendroglia are not very active metabolically) and contains no synapses, which have a high rate of substrate consumption.17 In addition, white matter is usually affected less than gray matter by metabolic depressants, such as general anesthesia,16 and events that reduce impulse conduction along spinal white matter tracts, such as spinal anesthesia18 and spinal shock,15 are associated with comparatively small metabolic effects on the conducting pathways. Thus, the fact that magnesium has a greater effect on spinal white than gray matter is unusual and the explanation is entirely speculative. Perhaps magnesium preferentially inhibits oligodendroglial function or nonsynaptic metabolic processes (such as axoplasmic transport). Alternatively, it is possible that the metabolic effect of magnesium is greater in spinal white than gray matter because magnesium uptake may be higher in white matter.

**Table 1. Physiologic Variables for Control and Hypermagnesemic Rats**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=5)</th>
<th>Hypermagnesemia (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>37.0±0.3</td>
<td>37.3±0.3</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>130±4</td>
<td>88±1*</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.47±0.06</td>
<td>7.34±0.03</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>118±10</td>
<td>102±12</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>37±2</td>
<td>37±2</td>
</tr>
</tbody>
</table>

*Values are mean±SEM. *p<0.01.

**Table 2. Spinal Glucose Utilization in Control and Hypermagnesemic Rats**

<table>
<thead>
<tr>
<th>Region</th>
<th>Control (n=5)</th>
<th>Hypermagnesemia (n=5)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray Matter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laminae I–III</td>
<td>38±1</td>
<td>31±1*</td>
<td>-26</td>
</tr>
<tr>
<td>IV–VI</td>
<td>47±2</td>
<td>35±2*</td>
<td>-35</td>
</tr>
<tr>
<td>VII</td>
<td>55±2</td>
<td>38±2*</td>
<td>-45</td>
</tr>
<tr>
<td>VIII</td>
<td>54±2</td>
<td>39±2*</td>
<td>-38</td>
</tr>
<tr>
<td>IX</td>
<td>52±2</td>
<td>37±2*</td>
<td>-38</td>
</tr>
<tr>
<td>White Matter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal</td>
<td>14±1</td>
<td>9±1*</td>
<td>-53</td>
</tr>
<tr>
<td>Lateral</td>
<td>28±1</td>
<td>17±1*</td>
<td>-63</td>
</tr>
<tr>
<td>Anterior</td>
<td>25±2</td>
<td>16±1*</td>
<td>-60</td>
</tr>
</tbody>
</table>

*Values are mean±SEM μmol/100 g/min. *p<0.01.
Insofar as its effect on spinal gray matter metabolism is concerned, magnesium appears to be very similar to general anesthesia. That is, in absolute terms, the glucose utilization of spinal gray matter during pentobarbital anesthesia and hypermagnesemia (Table 2) are nearly identical. Such is not the case for magnesium’s spinal white matter effects; glucose utilization is nearly 50% lower during hypermagnesemia (Table 2) than barbiturate anesthesia. Spinal metabolic depression, particularly and most prominently of spinal white matter, therefore appears to be a very plausible explanation for magnesium’s protective effect during experimental spinal ischemia. Moreover, even if some of magnesium’s other putatively beneficial properties, such as calcium channel blockade and relaxation of vascular smooth muscle, prove to be of greater significance during ischemia, the fact that magnesium profoundly reduces spinal metabolism is likely to be of additional benefit.

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References


Key Words • glucose • magnesium • spinal cord • rats
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