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Resistance artery vasodilation to magnesium sulfate during pregnancy and the postpartum state

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Euser, Anna G., and Marilyn J. Cipolla. Resistance artery vasodilation to magnesium sulfate during pregnancy and the postpartum state. *Am J Physiol Heart Circ Physiol* 288: H1521–H1525, 2005. First published December 2, 2004; doi:10.1152/ajpheart.00994.2004.—This study compared the vasodilatory responses to magnesium sulfate (MgSO_4) of cerebral and mesenteric resistance arteries and determined whether the responses varied between different gestational groups. Third-order branches ($<200 \mu\text{m}$) of the posterior cerebral (PCA) and mesenteric arteries (MA) were dissected from nonpregnant (NP; $n = 6$), late pregnant (LP; day 19, $n = 6$), and postpartum (PP; day 3, $n = 6$) Sprague-Dawley rats. A concentration-response curve was performed by replacing the low- MgSO_4 (1.2 mM) HEPES buffer solution with increasing concentrations of MgSO_4 (4, 6, 8, 16, and 32 mM) and measuring lumen diameter at each concentration. All groups exhibited concentration-dependent dilation to MgSO_4 , decreasing the amount of tone in the vessels. However, MA were significantly more sensitive to MgSO_4 than PCA. Whereas there was no difference in the response between different gestational groups in MA, the PCA from the LP and PP groups showed a significantly diminished response to MgSO_4 . The percent dilation at 32 mM MgSO_4 for PCA versus MA in NP, LP, and PP animals was 36 ± 2 vs. $51 \pm 7\%$ ($P < 0.05$), 19 ± 9 vs. $54 \pm 6\%$ ($P < 0.01$ vs. PCA and NP), and 12 ± 5 vs. $52 \pm 11\%$ ($P < 0.01$ vs. PCA and NP). These results demonstrate that MgSO_4 is a vasodilator of small resistance arteries in the cerebral and mesenteric vascular beds. The refractory responses of the PCA in LP and PP groups demonstrate changes in the cerebrovascular vasodilatory mechanisms with gestation. The greater sensitivity of the MA to MgSO_4 -induced vasodilation suggests that the prophylactic effect of MgSO_4 on eclamptic seizures may be more closely related to the lowering of systemic blood pressure than to an effect on cerebral blood flow.

eclampsia; cerebral arteries; mesenteric arteries; rat

HYPERTENSIVE DISORDERS OF PREGNANCY, including preeclampsia and eclampsia, affect $\sim 8\%$ of all pregnancies (19); however, the physician caring for a preeclamptic patient has few treatment options available from which to choose. Magnesium sulfate (MgSO_4) has been used empirically since the beginning of the 20th century to prevent seizures and continues to be used extensively as an eclampsia prophylactic (15, 22). Although the use of MgSO_4 is widespread and effective (2, 15, 16), its mechanism of action has historically been poorly understood. For example, studies have shown that it is a vasodilator of large conduit arteries such as the aorta (1, 14) and mesenteric rings (21); however,

its effects on the small resistance arteries that control systemic blood pressure and vascular resistance are not clear.

Resistance arteries ($<200 \mu\text{m}$ in diameter) operate in a state of partial constriction, or tone, and are generally the site of vascular resistance (9). This intrinsic tone also provides a set point from which arteries can constrict or dilate to control blood flow (9, 20). Thus the small resistance arteries have a great influence on peripheral vascular resistance and mean arterial pressure (20). In addition, because flow is dependent inversely on vessel diameter to the fourth power, small changes in luminal diameter lead to measurable changes in flow (12). It is therefore possible that as a vasodilator MgSO_4 prevents eclamptic seizures by lowering peripheral vascular resistance.

It was previously thought that eclampsia was due to vasospasm of cerebral vessels, and the resultant ischemia was the root of the neurological complications, which include headaches, nausea, vomiting, visual disturbances, and convulsions (23). This etiology seemed to be reinforced by studies that showed MgSO_4 dilated the middle cerebral artery (3, 4, 18). However, more recent evidence suggests that eclampsia is similar to hypertensive encephalopathy in which an acute elevation in blood pressure overcomes the myogenic vasoconstriction, causing forced dilatation of cerebral vessels, hyperperfusion, and edema (5, 8, 17, 23). Under these conditions, it would be paradoxical that a vasodilator, such as MgSO_4 , would be an effective prophylactic because it would cause greater hyperperfusion and promote further edema. We therefore hypothesized that there is a differential sensitivity to MgSO_4 between the cerebral and systemic resistance vessels such that the systemic circulation is more sensitive to MgSO_4 leading to a reduction in peripheral vascular resistance before vasodilation of cerebral vessels. To date, no studies have specifically compared the differential response of resistance arteries to MgSO_4 from cerebral and systemic circulations, important contributors to cerebral blood flow regulation and peripheral vascular resistance, respectively.

The goal of this study was to investigate the effects of MgSO_4 on small myogenic resistance arteries that play an integral role in the modulation of peripheral vascular resistance (mesenteric) and control cerebral blood flow (posterior cerebral). The effect of MgSO_4 was evaluated by directly measuring the luminal diameter of isolated and pressurized vessels, a powerful indicator of flow.

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Table 1. Percent constriction at different stages of gestation in response to $MgSO_4$

	Posterior Cerebral Artery		Mesenteric Artery	
	1.2 mM $MgSO_4$	32 mM $MgSO_4$	1.2 mM $MgSO_4$	32 mM $MgSO_4$
Nonpregnant	32±2	7±2†	38±3	5±1†
Late pregnant	26±6	14±5*	35±2	4±1†
Postpartum	13±5‡	3±3*	36±6	7±2†

Data are means ± SE. * $P \leq 0.05$ and † $P \leq 0.01$ vs. percent constriction in 1.2 mM $MgSO_4$; ‡ $P \leq 0.05$ vs. percent constriction of nonpregnant posterior cerebral arteries in 1.2 mM $MgSO_4$.

MATERIALS AND METHODS

Animals

Female Sprague-Dawley rats (Harlan) were used for all experiments and weighed 250–350 g. The animals were housed in the Animal Care Facility, an Association for Assessment and Accreditation of Laboratory Animal Care International accredited facility. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Vermont. Three groups of animals were compared: virgin nonpregnant (NP; $n = 6$), late pregnant (LP; day 19, $n = 6$), and postpartum (PP; day 3, $n = 6$). Both the LP and PP animals were studied in association with their first pregnancy.

Preparation of Arterial Segments and Pressurized Arteriograph System

The animals were decapitated after anesthesia with halothane-oxygen, and the brain quickly removed and transferred to cold physiological salt solution (HEPES buffer) at pH 7.4 ± 0.03 . A third-order branch of the posterior cerebral artery (PCA) was dissected, mounted on glass cannulas within a dual-chamber arteriograph, and secured with nylon sutures, as previously described (6). A branch of the PCA was chosen because the symptoms of eclampsia are focused in the occipital lobe and posterior region of the brain (10). A section of the small intestine was also quickly removed from the same animal so that experiments were paired. A third-order branch of the mesenteric artery (MA) was then dissected and similarly mounted on glass cannulas in the second chamber. Therefore, one PCA and one MA were studied simultaneously. Both proximal cannulas were attached to an in-line pressure transducer with a controller that allowed intravascular pressure to be maintained at a constant pressure or changed at a variable rate. The distal cannulas remained closed so that there was no flow through the arteries. With the use of an inverted microscope with an attached video camera and monitor connected to a video dimension analyzer (VDA), the lumen diameters were measured through optical windows in the bottom of the arteriograph chambers. A data-acquisition system was used to send the VDA and pressure output to a computer, which provided visualization of changes in diameters, similar to a chart recorder.

Experimental Protocol

Both vessels were equilibrated for 1 h at 50 mmHg in a 1.2 mM $MgSO_4$ HEPES buffer solution. Intravascular pressure was then increased to 75 mmHg, during which time both vessels developed spontaneous tone. However, because the amount of tone was less in the MA, it was precontracted with phenylephrine ($1 \times 10^{-7} - 5 \times 10^{-7}$ mM) until it attained a diameter of similar magnitude to that of the PCA. Both vessels were then exposed to increasing concentrations of $MgSO_4$, and the inner lumen diameter was recorded at each concentration (4, 6, 8, 16, and 32 mM). [The therapeutic range of $MgSO_4$ for seizure prophylaxis is 4–8 mg/dl (1, 9).] The vessels were then washed with 32 mM $MgSO_4$ HEPES solution. A single dose of

papaverine (0.1 mM) was added to each bath to obtain fully relaxed diameters. While vessels were exposed to papaverine, the pressure was reduced from 150 to 10 mmHg, and the lumen diameter was measured at each pressure (150, 125, 100, 75, 50, 40, 30, 20, and 10 mmHg).

Data Calculations

Percent change in diameter. The percent change in diameter was calculated as the difference in diameter from the vessel diameter at the baseline $MgSO_4$ concentration of 1.2 mM with the following equation: $[(\Phi - \Phi_{low\ mag})/\Phi_{low\ mag}] \times 100$, where Φ is the diameter at the respective concentration and $\Phi_{low\ mag}$ is the diameter in 1.2 mM $MgSO_4$.

Percent constriction. The percent constriction was calculated in both low-magnesium (1.2 mM $MgSO_4$) and high-magnesium (32 mM $MgSO_4$) solutions with respect to the vessel diameter in papaverine using the following formula: $[1 - (\Phi/\Phi_{papav})] \times 100$, where Φ is the vessel diameter and Φ_{papav} is the diameter in papaverine. All data are from vessels pressurized at 75 mmHg.

Drugs and Solutions

HEPES, papaverine, phenylephrine, and $MgSO_4$ were all purchased from Sigma. Papaverine (10^{-2} M) and phenylephrine (10^{-3} M) stock solutions were made weekly and stored at 4°C. All vessel experiments were conducted in a physiological salt solution composed of (in mM) 142.0 NaCl, 4.7 KCl, 1.2 $MgSO_4$, 0.50 EDTA, 2.8 $CaCl_2$, 1.0 HEPES, 1.2 KH_2PO_4 , and 5.0 glucose. A stock solution of 80 mM $MgSO_4$ was made daily in HEPES physiological salt solution.

Statistical Analysis

Data are expressed as means ± SE; n is the number of animals in each group. One MA and one PCA were taken from each animal. The differences in reactivity over gestation were determined using a one-way ANOVA followed by a Student-Newman-Keuls test for multiple comparisons. The difference between the vessels (MA vs. PCA) within gestational groups was determined using a paired t -test. Differences in constriction at the various concentrations were determined using a repeated-measure ANOVA.

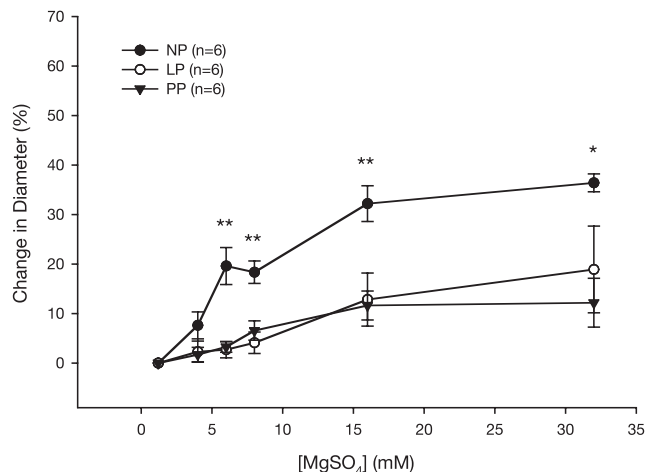


Fig. 1. Percent change in diameter of posterior cerebral artery (PCA) to increasing concentrations of magnesium sulfate ($MgSO_4$) at different stages of gestation: nonpregnant (NP), late pregnant (LP), and postpartum (PP) animals. Note that, while there is a concentration-dependent dilation in all groups, the PCA from LP and PP animals were less sensitive to $MgSO_4$ with respect to NP animals. * $P \leq 0.05$ and ** $P \leq 0.01$ vs. LP and PP.

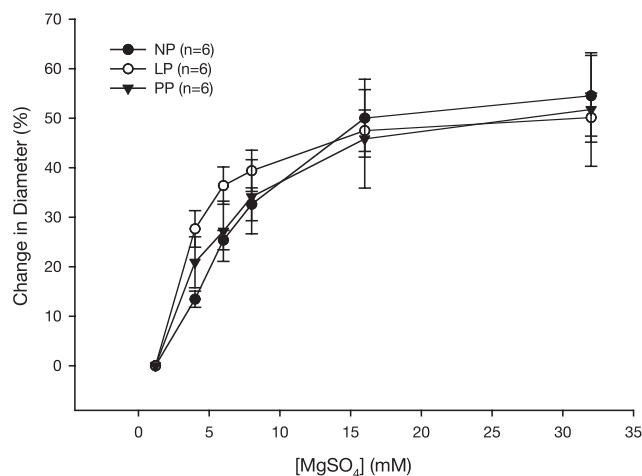


Fig. 2. Percent change in diameter of mesenteric arteries (MA) to increasing concentrations of $MgSO_4$ at different stages of gestation: NP, LP, and PP animals. The dilation was concentration-dependent and did not vary between gestational groups.

RESULTS

Table 1 shows the percent constriction of the vessels at different stages of gestation for PCA and MA in both low (1.2 mM) and high (32 mM) concentrations of $MgSO_4$ with respect to papaverine. The percent constriction was significantly less in high $MgSO_4$ versus low $MgSO_4$ concentrations in both vascular beds, demonstrating that $MgSO_4$ caused dilation. In addition, there was significantly less spontaneous tone in the PP versus NP PCA in 1.2 mM $MgSO_4$.

Figures 1 and 2 show the concentration-response curves to $MgSO_4$ in both PCA and MA, respectively, in all gestational groups. It is notable that the concentration-dependent response of the PCA was dampened in the LP and PP animals (Fig. 1). It is unlikely that this relates to the diminished tone in these vessels because the calculation normalizes the response to the start diameter. The dilation of the MA was similar between all groups (Fig. 2).

Across all gestational groups, the MA were more sensitive to $MgSO_4$ than PCA from the same animals at all concentrations. These results are shown in Figs. 3-5, with each figure showing

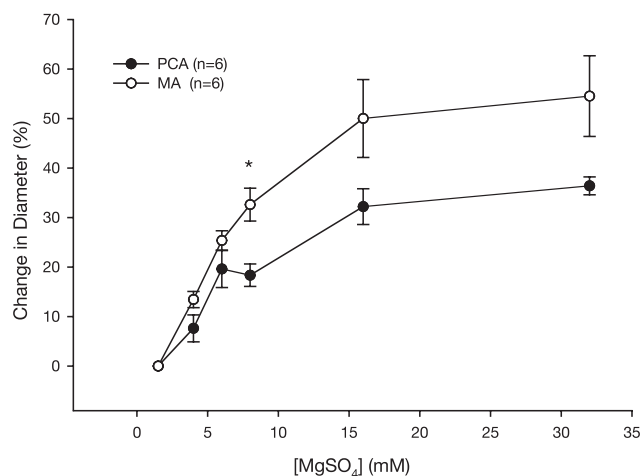


Fig. 3. Percent change in diameter of PCA and MA in NP animals in response to increasing concentrations of $MgSO_4$. * $P \leq 0.05$ vs. PCA.

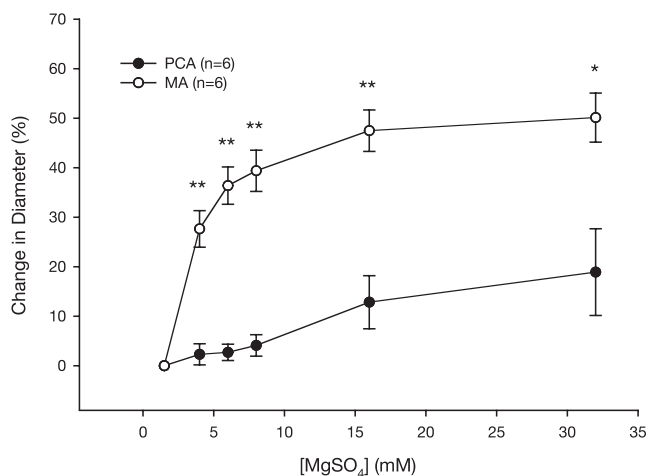


Fig. 4. Percent change in diameter of PCA and MA in LP animals in response to increasing concentrations of $MgSO_4$. Note that the MA was significantly more sensitive to $MgSO_4$ than the PCA. * $P \leq 0.05$ and ** $P \leq 0.01$ vs. PCA.

a different gestational stage. In both LP and PP animals, there was a significant difference in sensitivity between the two vascular beds (Figs. 4 and 5). For the NP animals (Fig. 3), although a difference between vascular beds was observed, it was not statistically significant at all concentrations.

DISCUSSION

The results of this study demonstrate that $MgSO_4$ has a concentration-dependent vasodilatory effect on resistance arteries of the cerebral and mesenteric vascular beds. However, the sensitivity of this response was dependent on the vascular bed and the gestational stage of the animal. For example, the PCA from LP and PP animals showed a refractory response to $MgSO_4$ compared with the NP group. This gestational change in reactivity was not observed in the MA. While it is not clear as to what the cause of this differential response was, it may be due to changes in the cerebrovascular vasodilatory mechanisms that have been demonstrated during pregnancy and the PP state (7).

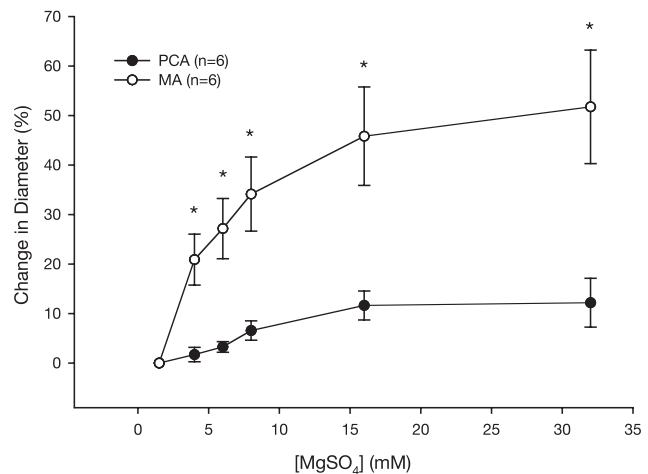


Fig. 5. Percent change in diameter of PCA and MA in PP animals in response to increasing concentrations of $MgSO_4$. Note that the MA is significantly more sensitive to $MgSO_4$ than the PCA. * $P \leq 0.05$ vs. PCA.



Studies have shown a vasodilatory effect with $MgSO_4$ treatment on both the cerebral circulation and systemic arteries (1, 3, 4, 12, 15, 21). Belfort et al. (4) investigated the effect of $MgSO_4$ on the cerebral circulation in patients with pregnancy-induced hypertension and showed a significant increase in mean velocity in the maternal middle cerebral artery in response to intravenous $MgSO_4$ that was interpreted as distal artery vasodilation. The present study is the first to directly examine the dilatory response of small distal cerebral arteries to $MgSO_4$ and found that it caused modest vasodilation, a response that differed with gestational stage (12–36%), shown in Fig. 1. In addition, this study also demonstrated that the systemic circulation (i.e., the mesenteric vascular bed) was more sensitive to $MgSO_4$ than the cerebral circulation (12–19% vs. 50–52%), especially in LP and PP animals, as seen in Figs. 4 and 5. This finding suggests that as an eclamptic seizure prophylaxis the effects of $MgSO_4$ may be more closely related to an effect on peripheral vascular resistance and lowering of systemic blood pressure than to an effect on cerebral blood flow. In support of this theory, it has been shown that treatment with a 6 g intravenous loading dose of $MgSO_4$ caused a significant decrease in both maternal systolic and diastolic blood pressures (4).

Because of the difference in the amount of intrinsic tone in MA versus PCA, we precontracted MA with phenylephrine to match the degree of constriction of PCA. While there was a significant decrease in myogenic tone in the PP PCA, we chose not to precontract those vessels for consistency within the group. It is important to note the possibility that $MgSO_4$ may dilate precontraction to phenylephrine more easily than myogenic tone, accounting for the increased sensitivity of the MA. Previous studies have shown a differential dilatory response of aortic rings from pregnant rats that depended on the method of precontraction (KCl vs. phenylephrine). However, $MgSO_4$ had a decreased vasodilatory action on vessels precontracted with phenylephrine compared with those precontracted with KCl (1). This suggests that the difference in dilation of the PCA versus the MA in our study could become even more significant if KCl was used for precontraction or if we compared dilation of intrinsic tone only.

$MgSO_4$ has been shown to have effects other than those on the vasculature that may relate to its effectiveness in preventing eclamptic seizures. Mg^{2+} has been shown to be a *N*-methyl-D-aspartate receptor antagonist (13), and it has been hypothesized that this interaction accounts for the anticonvulsant properties of $MgSO_4$. It is not clear whether or not $MgSO_4$ can cross the blood-brain barrier. However, if the blood-brain barrier has been disrupted due to the endothelial damage caused by acute hypertension, $MgSO_4$ could enter the brain parenchyma and exert its effects. Along these lines, Mg^{2+} has been shown to be protective of the blood-brain barrier under conditions that promote disruption (11), which could perhaps slow the progression of hypertensive encephalopathy. It is likely then that the prophylactic effect of $MgSO_4$ in preventing eclamptic seizures is multifactorial, encompassing both vascular and neurological mechanisms.

In conclusion, we found a significant difference in the vasodilatory effect of $MgSO_4$ on cerebral resistance arteries

from LP and PP animals compared with NP animals, implying that there are changes in the cerebrovascular vasodilatory mechanisms that occur with pregnancy. The LP and PP PCA were also significantly less sensitive to $MgSO_4$ than the MA, suggesting a differential action on mesenteric versus cerebral resistance arteries.

GRANTS

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