Magnesium sulfate ameliorates maternal and fetal inflammation in a rat model of maternal infection

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OBJECTIVE: Magnesium sulfate is proposed to have neuroprotective effects in the offspring. We examined the effects of maternal magnesium sulfate administration on maternal and fetal inflammatory responses in a rat model of maternal infection.

STUDY DESIGN: Pregnant rats were injected with saline, Gram-negative bacterial endotoxin lipopolysaccharide or lipopolysaccharide with magnesium sulfate (pre- and/or after lipopolysaccharide) to mimic infection. Maternal blood, amniotic fluid, fetal blood, and fetal brains were collected 4 hours after lipopolysaccharide and assayed for tumor necrosis factor, interleukin-6, monocyte chemotactic protein-1, and growth-related oncogene-KC. In addition, the effect of magnesium sulfate on cytokine production by an astrocytoma cell line was assessed.

RESULTS: Lipopolysaccharide administration induced tumor necrosis factor, interleukin-6, monocyte chemotactic protein-1, and growth-related oncogene-KC expression in maternal and fetal compartments. Maternal magnesium sulfate treatment significantly attenuated lipopolysaccharide-induced multiple proinflammatory mediator levels in maternal and fetal compartments.

CONCLUSION: Antenatal magnesium sulfate administration significantly ameliorated maternal, fetal, and gestational tissue-associated inflammatory responses in an experimental model of maternal infection.

Key words: chemokines, cytokines, fetal brain damage, GRO-KC, magnesium sulfate, maternal infection, MCP-1, neuroprotection, preterm labor

Preterm birth is a major cause of perinatal morbidity and accounts for approximately 70% of all perinatal mortality. Maternal infection, a major risk factor for preterm labor, is associated with significant neonatal morbidity, including neurologic injury. The maternal inflammatory response to infection is characterized by the production of proinflammatory mediators such as cytokines and chemokines, which can lead to tissue injury when produced in excess.

Lipopolysaccharide (LPS), the Gram negative bacterial endotoxin, has been used in laboratory animals to characterize the underlying pathogenesis of inflammation/infection-mediated preterm labor, to investigate infection-associated fetal neuronal damage, and to test various potential therapeutic interventions. Endotoxin administration to pregnant laboratory animals induces proinflammatory mediator production in the maternal and fetal compartments. This model mimics the elevated levels of cytokines and chemokines (eg, tumor necrosis factor-alpha [TNF], interleukin-6 [IL-6], monocyte chemotactic protein [MCP-1, CCL2]) observed in maternal and fetal compartments during infection and/or preterm laboring humans. Excessive and sustained inflammatory mediator production is proposed to activate the prostaglandin cascade leading to preterm birth, a risk factor for neurologic damage. In addition, fetal exposure to inflammatory mediators is understood to be linked to neurologic insults in the offspring, including long-term neurocognitive dysfunction and cerebral palsy.

Several reports support the neuroprotective effect of magnesium sulfate (MgSO4) in the fetus. A randomized clinical trial by Rouse and colleagues showed a significantly lower rate of cerebral palsy among infants born to women at 24-31 weeks’ gestation who received MgSO4 tocolysis for preterm labor. A recent metaanalysis also supported this association. Although MgSO4 has been used in obstetrics for suppressing preterm labor, its exact mechanism of action is unknown. Research in our laboratory revealing that MgSO4 attenuated cytokine production by cultured endothelial cells highlights the antiinflammatory activity of MgSO4. Additional in vivo studies demonstrating exaggerated inflammatory responses in Mg-deficient animals in the absence and presence of LPS further support the antiinflammatory effects of MgSO4.
MgSO₄ treatment suppresses cytokine and chemokine concentrations in maternal serum 90 min post-LPS

**A.** TNF, **B.** IL-6, **C.** MCP-1, and **D.** GRO-KC concentrations were measured in the maternal serum 90 minutes after saline or LPS injection (in the presence or absence of MgSO₄ treatment). Data are shown as individual data points (●) with geometric means (—).

**Figure 1**

Given the emerging evidence for (1) the association between neuronal injury and cytokine-mediated damage in the fetus, (2) the potential protective role of antenatal MgSO₄ therapy on the development of cerebral palsy, and (3) the antiinflammatory activity of MgSO₄, we sought to investigate the effects of MgSO₄ on cytokine and chemokine concentrations within maternal and fetal circulation, as well as in the amniotic fluid and fetal brain using a rodent model of LPS-induced maternal systemic infection, and to examine the effects of MgSO₄ on inflammatory mediator production by a human neuronal cell line.

**Materials and Methods**

We obtained approval from the Institutional Animal Care and Use Committee (IACUC) before conducting our study. Timed pregnant Sprague-Dawley rats (E9 and E11) (Charles River, Wilmington, MA) were housed individually under normal environmental conditions with free access to standard rat chow and water for at least 3 days before experimentation. LPS (strain *Escherichia coli* 055:B5) was purchased from Sigma-Aldrich (St. Louis, MO). MgSO₄ was purchased from APP Pharmaceuticals, LLC (Schaumburg, IL). Pregnant rats (gestational day 19) were randomly assigned by a technician blinded to the study design into 1 of 5 treatment groups (n = 6 per group): (1) saline (given subcutaneously [sc] q20 minutes for a period of 4 hours before and a period of 4 hours after saline intraperitoneally [ip]) (SSS) negative controls; (2) LPS (1 mg/kg, ip) and saline (sc q20 minutes for a period of 4 hours before and a period of 4 hours after LPS) (SLS) to mimic infection-associated preterm labor; (3) LPS (1 mg/kg, ip) and MgSO₄ (270 mg/kg load and then 27 mg/kg sc q20 minutes 4 hours before LPS only and saline given sc q20 minutes 4 hours after LPS) (MLS); or (5) LPS (1 mg/kg, ip) and saline given sc q20 minutes for a period of 4 hours before LPS and MgSO₄ (270 mg/kg load and then 27 mg/kg sc q20 minutes) for 4 hours after LPS (SLM). A similar MgSO₄ regimen was used by Hallak et al. Maternal blood was drawn (retroorbitally) 1½ hours after ip administration of LPS or saline. Four hours post-LPS (or saline) injection, the dams were euthanized by CO₂ (1 group of rats were euthanized 90 minutes post-LPS for fetal brain messenger RNA [mRNA] studies). Maternal blood was collected via cardiac puncture, and amniotic fluid was collected from each gestational sac. Fetal blood (pooled from the pups of each dam) and brains were obtained at the time of decapitation. Blood specimens were collected in nonheparinized tubes, the blood was allowed to clot for 30 minutes, and then specimens were centrifuged to collect serum. Fetal brains were flash frozen in liquid nitrogen, and both brain and serum samples were stored at −80°C.

Magnesium (Mg) concentrations of maternal blood and amniotic fluid were assessed by the North Shore-LIJ Health System Core Laboratories. For cytokine assessment, fetal rat brains were homogenized in 4 volumes of phosphate-buffered saline (PBS) containing 0.1% NP-40 and protease inhibitors. Cytokines/chemokines (TNF, IL-6, MCP-1, and growth-related oncogene-KC [GRO-KC, CXCL1]) in the rat serum, amniotic fluid, and brain homogenates were analyzed using Luminex XMAP technology (Millipore, St. Louis, MO). Fetal brain cytokine/chemokine concentrations were adjusted for protein concentrations (Bio-Rad protein method, Hercules, CA). Cytokine data are shown as individual data points with geometric means. The sensitivities (pg/mL) of the assays were as follows: TNF: 4.88–24.4; IL-6: 9.8–24.4; MCP-1: 3.81–4.88; and GRO-KC: 2.06–18.44 and the precisions (intraassay/interassay, %CV) were as follows: TNF: 9.16/11.1;
IL-6: 10.37/14.3; MCP-1: 3.81/16.5; and GRO-KC: 7.39/14.1.

The RNA was isolated from frozen fetal brains (at 90 minutes and 4 hours post-LPS) using the RNeasy kit (Qiagen, Valencia, CA) and RNA preparations with A260:280 ratios >1.9 were analyzed. The relative expression of GRO-KC, MCP-1, and CXCR2 mRNAs were assessed by quantitative real-time polymerase chain reaction (Q-PCR) using Roche Universal Probe Library technology. Reactions (performed in duplicate) were completed using 200 ng RNA, Eurogentec onestep qRT-PCR master mix, and 7900HT Fast Real-Time PCR for MCP-1, IL-6, and GRO-KC concentrations were measured in maternal serum 4 hours after saline or LPS injection (in the presence of absence of MgSO4 therapy). Data are shown as individual data points (●) with geometric means (–).

Statistical analyses

The rat cytokine data (normalized by a log transformation) was analyzed in 2 steps. First, 2-sample t-tests, using a log transformation of the cytokine levels, were used to compare the SSS (negative control) group with the SLS (positive control) group to confirm induction by LPS (P < .05). In step 2, separate 1-way analysis of variances (ANOVA) model was used to analyze the cytokines concentrations in the maternal and fetal compartments. On significant ANOVA findings (P < .05), each group (MCS, LMS, and MLM) was compared with the positive control group (SLS) using the Dunnett’s test. The standard assumptions of Gaussian residuals and equality of variance were tested. Q-PCR data were analyzed with ANOVA and significance set at P < .05.

RESULTS

At 90 minutes after maternal LPS administration (SLS) (when serum TNF levels peak), we observed a significant induction of TNF (P < .0001), IL-6 (P < .0292), MCP-1 (P < .0007), and GRO-KC (P < .0001) levels in the maternal serum when compared with control animals (SSS) (Figure 1, A-D). Treatment of pregnant animals with MgSO4 pre- and post-LPS (MLM) significantly decreased LPS-induced TNF (P < .0002), IL-6 (P < .0289), MCP-1 (P < .0234), and GRO-KC (P < .0026) levels in the maternal blood at 1½ hrs post-LPS compared with saline-LPS treated animals (SLS) (Figure 1, A-D). No significant reductions in serum inflammatory cytokines were observed when MgSO4 was given only before (MLS) or only after LPS treatment (SLM).

As expected, the levels of inflammatory mediators (TNF, P < .0002; IL-6, P < .0001; MCP-1, P < .0019; and GRO-KC, P < .0001) remained significantly elevated in the maternal serum when assessed 4 hours post-LPS (SLS) compared with controls (SSS) (Figure 2, A-D). Consistent with the results at 90 minutes post-LPS, we found that maternal treatment with MgSO4 (pre- and post-LPS, MLM) significantly decreased TNF (P < .0002).
Antenatal MgSO₄ administration attenuates proinflammatory mediator concentrations found in the amniotic fluid 4 hours post-LPS

A, TNF, B, IL-6, C, MCP-1, and D, GRO-KC concentrations were measured in amniotic fluid at 4 hours after saline or LPS injection (in the presence of absence of MgSO₄ therapy). Data are shown as individual data points (▾) with geometric means (——).ographics were as follows: SSS: 2.86 ± 0.23; SLS: 3.13 ± 0.18; MLM: 3.87 ± 0.28 (P < .002 vs SLS); MSL: 3.48 ± 0.2414; SLM: 3.73 ± 0.16.

Similar to our observations with cytokines in the amniotic fluid, we found that LPS administration (SLS) significantly increased fetal serum TNF, IL-6, MCP-1, and GRO-KC levels (assessed 4 hours post-LPS) when compared with saline-treated control animals (SSS) (Figure 4, A-D). At 4 hours post-LPS maternal administration, TNF, IL-6, and MCP-1 levels were significantly lower in the fetal blood (Figure 4) compared with (1) maternal blood levels (P < .01, P < .01, P < .001 for TNF, IL-6, and MCP-1, respectively, Figure 2) and (2) amniotic fluid levels of IL-6 (P < .001) and MCP-1 (P < .02) (Figure 3). Although fetal serum concentrations of IL-6 and GRO-KC were reduced in response to MgSO₄ treatment (MLM), only fetal serum TNF (P < .0281) levels were significantly decreased by MgSO₄ when administered pre- and post-LPS (MLM) when compared with saline-LPS treated animals (SLS) (Figure 4, A). Fetal blood volumes were too low to assess Mg concentrations.

Proinflammatory cytokine expression is elevated within the fetal brain after maternal LPS administration. In our study, only MCP-1 and GRO-KC levels were significantly induced within the fetal brain 4 hours post-LPS (Figure 5, A, B). MgSO₄, when given pre- and post-LPS (MLM) significantly reduced GRO-KC levels compared with saline-treated control animals (Figure 5, B). Maternal MgSO₄ treatment pre-/post-LPS injection (MLM) reduced fetal brain MCP-1 levels (5.4-fold); however, this reduction was not statistically significant (P = .056). By contrast, MgSO₄ therapy significantly attenuated fetal brain MCP-1 concentrations when administered only before LPS (MLS) (Figure 5, A).

Next, we investigated whether the inhibitory effect of MgSO₄ on chemokine protein concentrations was due to reduced chemokine mRNA expression within the fetal brain. MCP-1 mRNA ex-

Consistent with previous studies demonstrating that maternal infections trigger fetal inflammatory responses, we observed a significant induction of TNF (P < .0098), IL-6 (P < .0001), MCP-1 (P < .0032), and GRO-KC (P < .0001) in the amniotic fluid 4 hours after maternal LPS administration (Figure 3, A-D). Amniotic fluid levels of TNF, IL-6, and MCP-1 (Figure 3) were approximately 8- to 10-fold lower than those observed in maternal blood (P < .01, P < .01, P < .001 for TNF, IL-6, and MCP-1, respectively, Figure 2), whereas amniotic GRO-KC levels were similar to maternal blood concentrations. TNF (P < .0076), IL-6 (P < .0047), MCP-1 (P < .0036), and GRO-KC (P < .006) levels in the amniotic fluid significantly declined in response to antenatal MgSO₄ therapy when administered pre- and post-LPS (MLM) (Figure 3, A, B, D) and only amniotic GRO-KC levels were significantly lower when MgSO₄ was given before LPS injection only (MLS) (P < .0420) compared with the saline-LPS-treated animals (SLS) (Figure 3, D). Amniotic fluid Mg concentrations (mg/dL) at 4 hours after saline or LPS treatment were as follows: SSS: 2.86 ± 0.23; SLS: 3.13 ± 0.18; MLM: 3.87 ± 0.28 (P < .002 vs SLS); MSL: 3.48 ± 0.2414; SLM: 3.73 ± 0.16.

When compared with saline-LPS treated animals (SLS) (Figure 2, A). Maternal serum Mg concentrations (mg/dL) at 4 hours post-LPS were as follows: SSS: 2.6 ± 0.52; SLS: 3.0 ± 0.84; MLM: 6.067 ± 1.89 (P < .05 vs SLS); MSL: 4.03 ± 1.32; SLM: 10.5 ± 2.85 (P < .001 vs SLS). (MgSO₄ was first given as a bolus, followed by serial injections once every 20 minutes, as described in the Materials and Methods section.)
pression within the fetal brain was significantly increased 4 hours after maternal LPS (Figure 5, C) and MgSO4, when given pre- and post-LPS (MLM), significantly downregulated LPS-induced fetal brain MCP-1 mRNA expression (by approximately 3-fold, \( P < .05 \)) (Figure 5, C) 4 hours post-LPS. Although the mRNA expression of GRO-KC and its receptor, CXCR2, were not upregulated within the fetal brain after maternal LPS administration (data not shown), fetal brain GRO-KC mRNA expression was significantly induced 90 minutes post-LPS injection (Figure 5, D). However, MgSO4 treatment (MLM) only slightly reduced LPS-induced GRO-KC mRNA expression (\( P = .187 \)) within the fetal brain.

To better understand whether MgSO4 directly regulated chemokine production in the brain, we used a human astrocyte cell line (U87-MG) to examine the effects of MgSO4 on MCP-1 and IL-8 (a CXC chemokine family member homologous to rat GRO-KC). TNF or IL-1β stimulation significantly induced both MCP-1 and IL-8 production (Figure 6, A-D). Treatment of U87-MG cells with MgSO4 significantly reduced TNF-induced MCP-1 levels in a dose-dependent manner (Figure 6, A), but not TNF-induced IL-8 levels (Figure 6, B). Treatment with MgSO4 significantly reduced IL-1β-induced MCP-1 and IL-8 production by the neuronal cell line (Figure 6, C, D).

**COMMENT**

Despite major research efforts, the incidence of preterm births has increased by approximately 20% over the past 20 years and constitutes 12.8% of all live births in the United States.29 Several factors contribute to preterm births, including social stress, genetics, and infections, as well as proinflammatory mediators (eg, TNF, IL-6, IL-8) produced within the maternal and fetal compartments.1,5,30 Survivors of preterm birth are at increased risk of severe disabilities including bronchopulmonary dysplasia, retinopathy, neurocognitive impairment, and cerebral palsy.5,18,30 Using a rat endotoxin model of maternal infection-associated preterm labor, we observed the induction of proinflammatory cytokines (TNF and IL-6) and chemokines (MCP-1 and GRO-KC) in both maternal and fetal compartments after maternal LPS exposure. We report that maternal administration of MgSO4 significantly reduces proinflammatory mediator levels in both maternal and fetal compartments, including the fetal brain.

Animal models of endotoxin-induced preterm labor mimic the unregulated maternal and fetal inflammatory responses observed during maternal infection in humans. Maternal serum and amniotic fluid TNF levels, as well as TNF expression in the amnion, chorion, and decidua31,32 are upregulated in women presenting in labor. Consistent with these observations, the injection of TNF induces preterm labor in experimental animals.33 Likewise, elevated maternal serum, fetal plasma, and amniotic fluid IL-6 levels are linked to the onset of labor.1,34-36 MCP-1, a chemoattractant protein for monocytes and other leukocytes, is proposed to play an important role in preterm labor by promoting the influx of monocytes into the myometrium, cervix, and fetal membranes just before the initiation of parturition, and increased MCP-1 concentrations in gestational tissues and amniotic fluid are linked to preterm labor in humans.38-40 CXCL1 (GRO-α), known as GRO-KC in rodents, is a neutrophil chemoattractant induced during endotoxemia.41 CXCL1 within the amniotic fluid is a potential marker of intraamniotic infections in humans.42

Consistent with previous rodent studies,5,9,43,44 we found that maternal LPS administration significantly induced cytokine production in maternal and fetal compartments. More specifically, we found that LPS increased TNF, IL-6, MCP-1, and GRO-KC levels in maternal blood (Figures 1 and 2), amniotic fluid...
Our inability to detect LPS-induced TNF and IL-6 proteins in fetal brains 4 hours after maternal LPS injection might have resulted from using brain homogenates rather than immunostaining of neuronal tissue sections and/or using 1 time point for assessment (4 hours post-LPS). However, our results are consistent with previous reports that detected only TNF mRNA transcripts (not protein) in fetal brains.60,61 Finally, our study did not assess preterm birth nor did we measure “injury” in the fetal brains. Therefore, we are unable to conclude that maternal MgSO4 administration protects against LPS-induced preterm birth or brain injury in rat offspring.

In addition to elucidating the pathogenesis underlying infection- and inflammation-mediated preterm labor and poor neonatal outcome, experimental models can be used to test interventions (eg, antibiotics, progesterone, and IL-10).11-13 Antenatal MgSO4 administration targeted multiple cytokines and chemokines in both maternal and fetal compartments associated with preterm labor in this model and was most effective when given pre- and post-LPS probably because it accumulated in each compartment prior to “infection,” with the greatest effect in the maternal compartment. Given the strong association between the elaboration of proinflammatory mediators and the activation of the prostaglandin cascade within the gestational tissues as a mechanism for preterm parturition, we hypothesize that the tocolytic effects of MgSO4 could be attributed, in part, to its suppression of this response. Our observations showing that antenatal MgSO4 treatment reduced endotoxin-mediated inflammation in maternal and fetal compartments are consistent with studies by Hallak et al25 describing the protective effects of MgSO4 in models of hypoxia-induced fetal brain damage, and more recently, Burd et al14 revealing the neuroprotective effects of MgSO4 in LPS-mediated fetal brain damage. Several notable differences distinguish our study from that of Burd et al51: (1) we examined the effects of maternal MgSO4 administration on multiple inflammatory mediators (cytokines and chemokines) within both maternal serum, amniotic fluid, fetal blood, and fetal brain rather than fetal brains alone; (2) we used a systemic maternal infection model rather than a localized (intrauterine) infection model; (3) we measured inflammatory protein levels rather than mRNA transcripts; and (4) we used rats instead of mice. Together, these data support the overall protective and antiinflammatory effects of maternal MgSO4 administration on fetal and maternal responses and we hypothesize that MgSO4 therapy may exert neuroprotective effects in rat offspring similar to that observed in humans.19-21,52

Our findings are potentially important given the link between Mg deficiency and inflammation. Mg deficiency is associated with numerous conditions, including bacterial infections,53-54 generalized inflammation,55-57 and increased blood brain barrier permeability during sepsis.58

**FIGURE 5**

MgSO4 therapy alters chemokine concentrations and expression in the fetal brain 4 hours after maternal LPS administration.

A and B, Fetal brain chemokine concentrations (MCP-1, A, and GRO-KC, B) were measured in brain homogenates at 4 hours after saline or LPS injection (± MgSO4). Data are shown as individual data points () with geometric means (—), corrected for protein concentrations. A and B, + indicates P < .05 comparing SSS to SLS, or SLS to either MLM or MLS. C, Fetal brain MCP-1 mRNA expression measured by Q-PCR at 4 hours after saline or LPS. D, Fetal brain GRO-KC mRNA expression measured by Q-PCR at 90 minutes after saline or LPS (± MgSO4). C and D, + indicates P < .05 comparing SSS to SLS or SLS to MLM; # indicates P = .06.

GRO-KC, growth-related oncogene-KC; IL-6, interleukin-6; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein; MgSO4, magnesium sulfate; MLM, MgSO4-LPS-MgSO4; MLS, MgSO4-LPS-saline; MSL, MgSO4-saline-saline; Q-PCR, quantitative real-time polymerase chain reaction; SLS, saline-LPS-saline; SLM, saline-LPS-saline-saline; SSS, saline-saline-saline.


A and B. Fetal brain chemokine concentrations (MCP-1, A, and GRO-KC, B) were measured in brain homogenates at 4 hours after saline or LPS injection (± MgSO4). Data are shown as individual data points () with geometric means (—), corrected for protein concentrations. A and B, + indicates P < .05 comparing SSS to SLS, or SLS to either MLM or MLS. C, Fetal brain MCP-1 mRNA expression measured by Q-PCR at 4 hours after saline or LPS. D, Fetal brain GRO-KC mRNA expression measured by Q-PCR at 90 minutes after saline or LPS (± MgSO4). C and D, + indicates P < .05 comparing SSS to SLS or SLS to MLM; # indicates P = .06.

GRO-KC, growth-related oncogene-KC; IL-6, interleukin-6; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein; MgSO4, magnesium sulfate; MLM, MgSO4-LPS-MgSO4; MLS, MgSO4-LPS-saline; MSL, MgSO4-saline-saline; Q-PCR, quantitative real-time polymerase chain reaction; SLS, saline-LPS-saline; SLM, saline-LPS-saline-saline; SSS, saline-saline-saline.


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GRO-KC, growth-related oncogene-KC; IL-6, interleukin-6; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein; MgSO4, magnesium sulfate; MLM, MgSO4-LPS-MgSO4; MLS, MgSO4-LPS-saline; MSL, MgSO4-saline-saline; Q-PCR, quantitative real-time polymerase chain reaction; SLS, saline-LPS-saline; SLM, saline-LPS-saline-saline; SSS, saline-saline-saline.

Despite recommendations for pregnant women to consume additional Mg to compensate for maternal losses because of the demands of growing maternal and fetal tissues, several studies indicate insufficient Mg intake during pregnancy. Mg deficiency during pregnancy has been associated with early parturition and compromised fetal growth/development. Thus, we hypothesize that maternal Mg administration during maternal infection could suppress damaging inflammatory mediator production within the maternal and fetal compartments, including the fetal brain, to improve birth outcome. Future studies will be designed to test our hypotheses.

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