Effects of postnatal dexamethasone on blood-brain barrier permeability and brain water content in newborn lambs

GREGORY D. SYSYN,1 KATHERINE H. PETERSSON,1 CLIFFORD S. PATLAK,2 GRAZYNA B. SADOWSKA,1 AND BARBARA S. STONESTREET1

1Brown University School of Medicine, Department of Pediatrics, Women and Infants’ Hospital of Rhode Island, Providence, Rhode Island 02905; and 2Department of Surgery, State University of New York at Stony Brook, Stony Brook, New York 11794-8191

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Sysyn, Gregory D., Katherine H. Peterson, Clifford S. Patlak, Grazyna B. Sadowska, and Barbara S. Stonestreet. Effects of postnatal dexamethasone on blood-brain barrier permeability and brain water content in newborn lambs. Am J Physiol Regulatory Integrative Comp Physiol 280: R547–R553, 2001.—We showed that antenatal corticosteroids reduced blood-brain barrier permeability in fetuses at 60 and 80%, but not 90% of gestation, and decreased brain water content in fetuses. Our objective was to examine the effects of postnatal corticosteroids on regional blood-brain barrier permeability and brain water content in newborn lambs. Three dexamethasone treatment groups were studied in 3- to 5-day-old lambs. A 0.01 mg/kg dose was selected to estimate the amount of dexamethasone that might have reached fetuses via antenatal treatment of ewes in our previous studies. The other doses (0.25 and 0.5 mg/kg) were chosen to approximate those used clinically to treat infants with bronchopulmonary dysplasia. Lambs were randomly assigned to receive four intramuscular injections of dexamethasone or placebo given 12 h apart on days 3 and 4 of age. Blood-brain barrier function was measured by the blood-to-brain transfer constant (K) to α-aminobutyric acid, brain plasma volume was measured with polyethylene glycol for the calculation of K, and brain water was measured by wet-to-dry tissue weights. Postnatal treatment with corticosteroids did not reduce barrier permeability in newborn lambs. Blood brain volume was higher in the 0.25 and 0.5 mg/kg dose dexamethasone groups than in the placebo group. Brain water content did not differ among the groups. We conclude that postnatal treatment with corticosteroids did not reduce regional blood-brain barrier permeability or brain water content but increased the brain plasma volume in newborn lambs. These findings are consistent with our previous work indicating that barrier permeability is responsive to corticosteroids at 60 and 80% of gestation and brain water regulation at 60% of gestation, but not in term fetuses or newborn lambs.

α-aminobutyric acid; plasma cortisol; postnatal sheep

MATERNALLY ADMINISTERED ANTENATAL corticosteroids have been widely used to reduce the incidence of respiratory distress syndrome in low-birth-weight infants (25). Antenatal corticosteroids are now a routine part of the prenatal management of women in premature labor. This therapy has also been shown to facilitate the transition from fetal to neonatal life by its beneficial effects on multiple-organ systems (4, 28, 33). Antenatal corticosteroid administration has been reported to have an important role in lowering the risk of intraventricular hemorrhage in premature infants (15). These effects might be explained in part by accelerated vascular maturation.

Dexamethasone is also commonly used in premature infants to attenuate lung damage resulting from mechanical ventilation (23). Several studies have suggested that early postnatal treatment with dexamethasone may reduce chronic oxygen dependency, lessen lung inflammation, and improve lung function in premature infants with respiratory distress syndrome (38, 47, 49). However, recent findings also suggest that this treatment may be associated with developmental delay (46, 49). Nonetheless, the effects of dexamethasone on the newborn brain have not been well documented.

The blood-brain barrier is composed of a continuous layer of cerebrovascular endothelial cells joined by tight intercellular junctions (8, 9). This specialized barrier serves as an interface between the circulating blood, brain interstitium, and parenchyma, isolating brain tissue from blood constituents. Therefore, the blood-brain barrier maintains central nervous system (CNS) homeostasis by preventing entry of substances that might alter neuronal function in the CNS. Our laboratory previously demonstrated ontogenic decreases in blood-brain barrier permeability to α-aminobutyric acid (AIB) from 60% of fetal gestation through the newborn period and up to maturity in adult sheep, and the blood-brain barrier’s relatively impermeability to AIB in most brain regions of fetuses and lambs (43). Because the blood-brain barrier is relatively impermeable in the fetus and newborn, the barrier also protects the developing brain from factors that could impair neuronal function.

Evidence in adult rodents suggests that the blood-brain barrier is under hormonal control (17, 20, 50). Adrenalectomy increases blood-brain barrier permeability and...
ability, and corticosterone replacement reverses this effect on the barrier (20). Therefore, the pituitary-adrenal cortical axis may function as a physiological regulator of barrier function (20). In addition, pharmacological doses of dexamethasone have been reported to reduce barrier permeability in adult rodents (17, 36, 50). The effects of postnatal corticosteroids on blood-brain barrier function have not been studied in newborn subjects of any species.

The blood-brain barrier also serves to maintain electrolyte homeostasis within the brain by regulating the passage of sodium and other osmotic agents across the barrier and thereby preserving brain water balance (6, 7). In addition, dexamethasone treatment in adult rodents has been shown to affect water permeability across the blood-brain barrier (36). Several lines of evidence suggest that water and electrolyte homeostasis is regulated and matured by antenatal treatment with corticosteroids (4, 28, 41). This therapy accelerates renal functional maturation in premature fetuses and lambs (4, 41), as well as development of skin-surface lipidicity in premature rats (28), and regulates water and electrolyte homeostasis in premature infants (29).

Our laboratory previously showed that maternally administered exogenous antenatal corticosteroids reduced blood-brain permeability early, but not late, in fetal development and that increases in endogenous plasma cortisol concentrations were associated with decreases in regional blood-brain barrier permeability during fetal development (45). In addition, we have also shown that maternally administered antenatal corticosteroids exert age-related differential effects on fetal brain and nonneural tissue water contents (39).

Given the above considerations, the purpose of the current study was to examine the effects of postnatal corticosteroid treatment on regional blood-brain permeability and brain water content in newborn lambs. We examined the effect of three different dexamethasone treatment regimens (0.01, 0.25, and 0.5 mg/kg) in 3- to 5-day-old lambs. The 0.01 mg/kg dose was selected to approximate the amount of dexamethasone that might have reached fetuses via antenatal treatment of ewes in our previous studies (44, 45). This estimate takes into consideration that, even if only 1% of the maternal dose was to reach the fetus, the near-term fetus might receive a dose of 0.01 mg/kg, i.e., 6 mg × 0.01 ÷ 4–5 kg or the estimated weight of a near-term fetus. The other two doses were chosen to approximate those used clinically to treat premature infants with bronchopulmonary dysplasia (30, 35, 38, 47, 49). The lambs received four intramuscular injections of dexamethasone or placebo given 12 h apart on days 3 and 4 of age up to 18 h before the studies. In each treatment group, three additional lambs were studied to determine brain vascular volume with [14C]polyethylene glycol ([14C]PEG, Amersham).

Dexamethasone was chosen for our studies, because it is one of the most extensively studied corticosteroids for accelerating fetal maturation and has been widely used in experimental studies of the CNS, to treat CNS disorders and to attenuate the development of bronchopulmonary dysplasia (4, 17, 24, 25, 36, 47, 49, 50). We studied lambs in the early newborn period and used the same dexamethasone treatment regimen as in our previous studies to compare the findings in the lambs with our work in fetuses (39, 44, 45). In addition, a 12-h dosing interval is commonly used to attenuate the development of bronchopulmonary dysplasia in premature infants (47–49).

Experimental protocol and methodology. On day 5 of life, 12–18 h after the last dose of placebo or dexamethasone, the lambs were removed from the ewes and, after having been acclimatized to the laboratory for 1 h, were studied while blindfolded and quietly resting in slings. Blood-brain barrier function was measured in the lambs with [14C]AIB (DuPont-New England Nuclear, Boston, MA). The blood-to-brain transfer constant was measured as previously described (12, 27, 40, 42, 44, 45). After baseline physiological determinations were obtained, [14C]AIB was rapidly injected intravenously, and arterial plasma concentrations were obtained at fixed times before and after injection as follows: −1, 0.25, 0.5, 1, 2, 3, 5, 7, 9, 15, 25, 35, 45, 55, 60 min, and at termination 5 min after the end of the study. On the basis of our previous analysis of rate constants and exposure times for tracers in adult rats and mathematical analysis of AIB in fetal, premature, and newborn sheep, the 0.01 mg/kg dose and the 12-h dosing interval were chosen to approximate the plasma profile needed for calculation of the blood-to-brain transfer constant $K_{e}$, as described by Ohno et al. (27). In these experiments, the unidirectional $K_{i}$ was quantified for [14C]AIB in newborn lambs. Brain vascular volume was determined by giving [14C]PEG 2 min before the end of the experiment to three additional lambs in each treatment group.

AIB is a synthetic amino acid that is not present in mammalian tissues. This amino acid has been used extensively to measure accurately the total and regional blood-brain barrier
permeability in a variety of mammals, including fetal, premature, and newborn sheep (5, 40, 42–44, 50). The lambs received 12–30 μCi/kg of [14C]AIB or 20–25 μCi/kg of [14C]PEG. At the end of the study, the lambs were given intravenous pentobarbital sodium (10–20 mg/kg) to achieve a surgical plane of anesthesia and were decapitated to terminate immediately the blood flow to the brain. The brain was removed within 5 min for regional brain tissue samples. The brains were dissected into the following regions: cerebral cortex, caudate nucleus, hippocampus, cerebellum, thalamus, superior colliculus, inferior colliculus, pons, medulla, and cervical spinal cord. The cerebral cortex was further divided into frontal, parietal, and occipital cortices.

Tissue samples were treated as previously described (12, 42–45). Briefly, Solvable (Packard Instrument, Meridian, CT) was added to the vials containing the tissue samples, and the vials were then placed in a shaking water bath at 50°C overnight. Tissue sample decoloration was achieved with 30% hydrogen peroxide. Scintillation cocktail (Atomlight, DuPont-New England Nuclear) was added to each vial before the radioisotope was quantified with a TM Analytic Beta Counter (model 6895, Elk Grove Village, IL). All samples were corrected for background, sample spillover, and quenching. The plasma from the arterial blood samples was measured into scintillation vials, and the scintillation cocktail was added to each vial. The plasma radioactivity was quantified as described for the tissue samples.

The blood-to-brain $K_i$ (μl/g brain$^{-1}$.min$^{-1}$) is given by

$$K_i = A_{br} \int_{0}^{t} c_p(T) dT$$

where $A_{br}$ is the amount of tracer that crossed the blood-brain barrier from blood to brain during the tracer study (dpm/g) and $c_p$ is the concentration of tracer in plasma (dpm/μl) at the time $t$ (min). $A_{br}$ is obtained by correcting the total amount of isotope measured in the tissue, $A_m$ (dpm/g), for that residual part remaining in the brain vasculature at the termination of the experiment. Thus $A_{br}$ was obtained from the equation $A_{br} = A_m - V_p c_p$, where $V_p$ is the plasma volume of brain tissue (μl/g) and $c_p$ is the concentration of tracer in the terminal plasma sample (dpm/ml). $V_p = A_m / c_p$, where $A_m$ and $c_p$ have the same definitions as $A_m$ and $c_p$ above except that they apply to [14C]PEG (12).

Regional brain water was determined in the cerebrum, caudate nucleus, cerebellum, midbrain, and medulla. Brain regions were weighed immediately after autopsy to determine the fresh tissue weight. Tissue water concentration was determined by placing the regional brain tissue into preweighed dry vials, drying the tissues at 90°C to a constant weight, and reweighing the vials to attain the dry weight values (13, 40).

Arterial pH, blood gases, hematocrit, heart rate, and mean arterial blood pressure in the lambs were measured at baseline and 30 and 50 min of study. The lambs' arterial plasma osmolality and glucose and cortisol concentrations were measured before the end of the study. Heart rates and mean arterial blood pressures in the lambs were measured with pressure transducers (model 1280 C, Hewlett-Packard, Lexington, MA) and recorded on a polygraph (model 17758 B Series, Hewlett Packard). Blood gases and pH were measured on a Corning blood gas analyzer (model 238, Corning Scientific, Medford, MA) at 39°C. Hematocrit was measured in duplicate by the microhematocrit method. Plasma osmolality was measured in duplicate on a vapor pressure osmometer (Vapro model 5520, Wescor, Logan, UT), and glucose on

Table 1. Physiological, biochemical, and hormonal variables of the newborn lambs by study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>0.01</th>
<th>0.25</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.40±0.04</td>
<td>7.39±0.04</td>
<td>7.40±0.05</td>
<td>7.41±0.03</td>
</tr>
<tr>
<td>PaO$_2$, mmHg</td>
<td>100±15</td>
<td>94±21</td>
<td>96±13</td>
<td>89±8</td>
</tr>
<tr>
<td>PaCO$_2$, mmHg</td>
<td>43±5</td>
<td>43±6</td>
<td>43±3</td>
<td>39±4</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>34±4</td>
<td>33±4</td>
<td>31±7</td>
<td>33±4</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>260±33</td>
<td>224±60</td>
<td>236±47</td>
<td>222±38</td>
</tr>
<tr>
<td>MABP, mmHg</td>
<td>52±8</td>
<td>52±9</td>
<td>55±10</td>
<td>68±9†‡</td>
</tr>
<tr>
<td>Osmolality, mOsm/kgH$_2$O</td>
<td>296±10</td>
<td>297±5</td>
<td>302±5</td>
<td>300±16</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>138±12</td>
<td>117±19</td>
<td>165±45</td>
<td>213±128*</td>
</tr>
<tr>
<td>Cortisol, ng/ml</td>
<td>64±29</td>
<td>51±38</td>
<td>9±5†‡</td>
<td>22±26†‡</td>
</tr>
</tbody>
</table>

Values are means±SD. PaO$_2$ and PaCO$_2$, arterial oxygen and carbon dioxide tension, respectively; MABP, mean arterial blood pressure; $n$ = 11, placebo; $n$ = 6, 0.01 mg/kg dose; $n$ = 8, 0.25 mg/kg dose; and $n$ = 4, 0.5 mg/kg dose group. *$P < 0.05$ vs. values of placebo group, †$P < 0.05$ vs. values of 0.01 mg/kg group, and ‡$P < 0.05$ values of 0.25 mg/kg group.
gen tension, carbon dioxide tension, hematocrit, and heart rate values did not differ among the four treatment groups. Mean arterial blood pressure was higher in the 0.5 mg/kg dose dexamethasone treatment group. The plasma glucose concentrations were higher in the 0.5 than 0.01 mg/kg dose dexamethasone treatment group. Plasma cortisol concentrations were lower in the 0.25 and 0.5 mg/kg dose dexamethasone groups than the placebo and the 0.01 mg/kg dose dexamethasone treatment groups. The arterial pH, oxygen tension, carbon dioxide tension, base excess, hematocrit, heart rate, and mean arterial blood pressures values of the lambs did not change during the 1-h study in any treatment group.

The regional brain $K_i$ values for AIB of the placebo and dexamethasone treatment groups are illustrated in Fig. 1. The $K_i$ values did not differ among the placebo and the 0.01, 0.25, or 0.5 mg/kg dose dexamethasone treatment groups across the brain regions (ANOVA, main effects for treatment group: $F = 2.03, P = 0.14$). The $K_i$ values also did not differ among the treatment groups across the occipital, parietal, and frontal cortices (ANOVA, main effects for treatment group: $F = 1.54, P = 0.23$). The $K_i$ values for AIB exhibited significant regional heterogeneity within the placebo (ANOVA, main effects for regional $K_i$ values: $F = 82.2, P < 0.01$) and the 0.01 (ANOVA, main effects for regional $K_i$ values: $F = 16.0, P < 0.01$), 0.25 (ANOVA, main effects for regional $K_i$ values $F = 44.1, P < 0.01$), and 0.5 (ANOVA, main effects for regional $K_i$ values: $F = 13.8, P < 0.01$) mg/kg dexamethasone treatment groups.

The regional brain plasma volume values by study group are summarized in Table 2. Regional brain plasma volume was higher in the 0.25 and 0.5 mg/kg dexamethasone treatment groups than the placebo treatment group (ANOVA, main effects for 0.25 mg/kg dexamethasone versus the placebo treatment group: $F = 12.9, P < 0.05$). The regional brain water content values were not observed among the four treatment groups across the brain regions (ANOVA, main effects for treatment group: $F = 0.20, P = 0.90$).

### DISCUSSION

This study examined the effects of postnatal corticosteroid treatment on blood-brain barrier permeability and brain water content in newborn lambs. We examined the effect of three different dexamethasone treatment regimens. One regimen approximated the amount of dexamethasone (0.01 mg/kg) that might have reached the fetal sheep after maternal antenatal treatment in our previous studies (44, 45); with the two other regimens, we examined the effect of two different

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**Table 2. Brain plasma volume measured with polyethylene glycol by study group**

<table>
<thead>
<tr>
<th>Regions</th>
<th>Placebo</th>
<th>0.01</th>
<th>0.25</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td>21.9 ± 3.7</td>
<td>27.2 ± 3.3</td>
<td>37.0 ± 7.2</td>
<td>36.8 ± 8.4*</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>15.7 ± 3.5</td>
<td>20.1 ± 3.0</td>
<td>23.9 ± 0.7*</td>
<td>27.7 ± 4.6*</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>15.1 ± 3.9</td>
<td>20.5 ± 3.6*</td>
<td>21.4 ± 1.6*</td>
<td>22.6 ± 0.8*</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>23.7 ± 2.9</td>
<td>30.1 ± 3.8</td>
<td>38.8 ± 4.0*</td>
<td>41.6 ± 7.2*†</td>
</tr>
<tr>
<td>Thalamus</td>
<td>11.8 ± 3.3</td>
<td>16.2 ± 1.8</td>
<td>20.5 ± 3.2*</td>
<td>22.7 ± 4.1*</td>
</tr>
<tr>
<td>Superior colliculus</td>
<td>19.7 ± 6.2</td>
<td>22.6 ± 3.2</td>
<td>24.6 ± 2.0</td>
<td>22.8 ± 2.5</td>
</tr>
<tr>
<td>Inferior colliculus</td>
<td>25.0 ± 6.9</td>
<td>35.7 ± 7.1</td>
<td>27.1 ± 1.6</td>
<td>52.4 ± 4.2*‡</td>
</tr>
<tr>
<td>Pons</td>
<td>16.3 ± 4.0</td>
<td>23.7 ± 2.6*</td>
<td>23.7 ± 0.4*</td>
<td>22.2 ± 2.2*</td>
</tr>
<tr>
<td>Medulla</td>
<td>18.1 ± 4.8</td>
<td>22.8 ± 3.3</td>
<td>28.5 ± 7.0</td>
<td>28.1 ± 2.5</td>
</tr>
<tr>
<td>Cervical spinal cord</td>
<td>16.1 ± 5.8</td>
<td>18.4 ± 3.9</td>
<td>19.1 ± 3.8</td>
<td>25.7 ± 9.0</td>
</tr>
</tbody>
</table>

Values are means ± SD in μl/g brain. $n = 3$, placebo, 0.01, 0.25, and 0.5 mg/kg groups; *$P < 0.05$ vs. values of placebo group, †$P < 0.05$ vs. values of 0.01 mg/kg group, ‡$P < 0.05$ vs. values of 0.25 mg/kg group.

**Fig. 1.** The blood-to-brain transfer constant $K_i$ of the lambs in the placebo and the 0.01, 0.25, and 0.5 mg/kg dexamethasone treatment groups in 10 brain regions. The $K_i$ values did not differ among the placebo and the 0.01, 0.25, or 0.5 mg/kg dexamethasone treatment groups across the brain regions (ANOVA, main effects for treatment group: $F = 2.03, P = 0.14$). Values are means ± SD.
doses of dexamethasone (0.25 and 0.5 mg/kg), which are similar to those used clinically to treat premature infants with bronchopulmonary dysplasia (30, 35, 38, 47, 49). We found that postnatal treatment with corticosteroids did not reduce regional blood-brain barrier permeability or brain water content but increased regional brain plasma volume in newborn lambs. The present findings combined with those in our previous work (39, 44, 45) can be interpreted to suggest that, early in prenatal development, blood-brain barrier vasculature and brain water regulation appear to be responsive to exogenous corticosteroids and, later in the perinatal period, this responsiveness appears no longer to be present.

Postnatal dexamethasone treatment affected the metabolic, hormonal, and hemodynamic homeostasis of the newborn lambs. The lower plasma cortisol and elevated glucose concentrations suggest that dexamethasone suppressed the adrenocortical axis and caused glucose intolerance in the newborn lambs (10, 37). Likewise, postnatal dexamethasone treatment was associated with elevated mean arterial blood pressure in the lambs (10, 14, 22, 37). It should be pointed out that the decrease in plasma cortisol and increases in plasma glucose concentrations and mean arterial blood pressure were detected in the lambs 12–18 h after the last dose of dexamethasone. As outlined above, we used the same dexamethasone treatment regimen as in our previous studies to compare our findings in the lambs with those in the fetuses (39, 44, 45). We cannot rule out the possibility that these changes might have been greater if the determinations had been made during treatment and/or the lambs had been treated for a longer period of time similar to that used clinically to treat premature infants with bronchopulmonary dysplasia (30, 35, 38, 48).

We previously showed that maternally administered exogenous antenatal corticosteroids reduced blood-brain permeability at 60 and 80% of gestation, but not at 90% (44, 45). Our findings that antenatal corticosteroid treatment did not influence barrier permeability in near-term fetuses (45) are consistent with our findings in newborn lambs. Blood-brain barrier permeability was not reduced even after doses of 0.5 mg/kg were given to the lambs in the same regimen as we used in the ewes. However, pharmacological doses of dexamethasone have been reported to reduce blood-brain barrier permeability even in adult rodents (17, 36, 50).

Although the differences between our findings in newborn lambs compared with those in adult rodents (17, 36, 50) might be related to differences in species and treatment regimen, we cannot rule out the possibility that an even larger dose of dexamethasone might have reduced barrier permeability in the lambs. Our findings in fetal sheep and lambs suggest that corticosteroids reduce blood-brain barrier permeability in fetuses at 60 and 80% of gestation, but not in near-term fetuses or newborn lambs (44, 45).

We have also shown that increases in endogenous plasma cortisol concentrations during development were associated with decreases in regional blood-brain barrier permeability in the ovine fetus (45). Plasma cortisol concentrations increase during late gestation and surge within hours of birth (1, 11, 21). Plasma cortisol concentrations were elevated after birth in our placebo-treated newborn lambs. Therefore, the endogenous increases in corticosteroids before and after birth are most likely in part responsible for the reduced responsiveness of the barrier to exogenous corticosteroids in late-gestation fetuses and newborn lambs (45). Therefore, the age-related differential responsiveness of the fetal and neonatal blood-brain barrier to exogenous corticosteroids might be related to the influence of increases in endogenous corticosteroids upon barrier maturation.

Postnatal corticosteroid treatment is associated with increases in regional brain plasma volume in our newborn lambs. Our findings contrast with those in adult subjects with brain tumors, in which treatment with dexamethasone was associated with reductions in cerebral vascular blood volume (19, 24, 31). However, our results in lambs are consistent with findings in premature infants in which cerebral blood volume, measured by near-infrared spectroscopy, demonstrated short-term increases after treatment with dexamethasone (34). The mechanism for the increase in regional plasma volume after dexamethasone treatment cannot be determined from our study. However, increases in microvessel diameter and/or increased perfusion of a larger fraction of the microvessels (2, 3) might account for our findings.

Several lines of evidence suggest that water and electrolyte homeostasis are regulated and matured by antenatal treatment with corticosteroids (4, 28, 41). We previously showed that maternally administered antenatal corticosteroids exert age-related differential effects on fetal brain and nonneural tissue water con-

Table 3. Regional brain water distribution of the newborn lambs by study group

<table>
<thead>
<tr>
<th>Region</th>
<th>Placebo</th>
<th>Dexamethasone, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>5.01 ± 0.13</td>
<td>4.98 ± 0.20</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>4.85 ± 0.15</td>
<td>4.73 ± 0.36</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>4.32 ± 0.08</td>
<td>4.46 ± 0.36</td>
</tr>
<tr>
<td>Midbrain</td>
<td>3.88 ± 0.10</td>
<td>3.95 ± 0.12</td>
</tr>
<tr>
<td>Medulla</td>
<td>3.24 ± 0.09</td>
<td>3.23 ± 0.20</td>
</tr>
</tbody>
</table>

Values are means ± SD in ml/g dry wt brain. n = 6, 0.01 mg/kg dose except for caudate nucleus in which n = 5; n = 8, 0.25 mg/kg dose; and n = 4, 0.5 mg/kg groups.
tent (39). Nevertheless, postnatal treatment with corticosteroids did not affect regional brain water content in our newborn lambs. We cannot rule out the possibility that, if the lambs had been treated for a longer period of time, brain water content might have been affected (30, 35, 38, 48).

In summary, postnatal treatment with corticosteroids did not reduce regional blood-brain barrier permeability or brain water content but was associated with increases in regional brain blood volume in newborn lambs.

Perspectives

The pituitary-adrenal cortical axis appears to modulate blood-brain barrier permeability during development. The increases of plasma cortisol concentration during late gestation, which surge within hours of birth, and postnatal increases after birth are most likely responsible for the normal ontogenic decreases in barrier permeability that occur during normal fetal and neonatal maturation (43). We have shown that exogenous corticosteroids do not affect barrier permeability in near-term fetuses or newborn lambs (45). In these subjects, the normal ontogenic decreases in barrier permeability are most likely related to endogenous increases in corticosteroids. Therefore, it appears that, because of the exposure to elevations in endogenous corticosteroids, the blood-brain barrier is not responsive to exogenous corticosteroids. The overall significance of these findings is that the effect of endogenous corticosteroids on the developing blood-brain barrier may protect the CNS from elevations in systemic concentrations of glucose and other substrates (16, 18, 32) that could impair neuronal function at birth.

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REFERENCES


30. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver RG III, and Dillard RG. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. *Pediatrics* 104: 15–21, 1999.


