

# Effect of Steroids on Edema and Sodium Uptake of the Brain During Focal Ischemia in Rats

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Steroids reduce permeability of the blood-brain barrier and inhibit active sodium transport by brain capillaries *in vitro*. Since the rate of edema formation during the early stages of ischemia is related to the rate of sodium transport from blood to brain, this study was designed to determine whether steroids reduce ischemic edema formation by inhibiting blood-brain barrier sodium transport. Dexamethasone was compared with progesterone since the latter is a more potent inhibitor of sodium transport in isolated capillaries. Sprague-Dawley rats were treated with vehicle ( $n=22$ ) or 2 mg/kg of either dexamethasone ( $n=22$ ) or progesterone ( $n=17$ ) 1 hour before occlusion of the middle cerebral artery. After 4 hours of ischemia, brain water content and blood-brain barrier permeability to [ $^3\text{H}$ ] $\alpha$ -aminoisobutyric acid and sodium-22 were determined. In controls, mean  $\pm$  SEM water content of tissue in the center of the ischemic zone was  $82.4 \pm 0.2\%$ . Brain edema was significantly reduced following pretreatment with either dexamethasone ( $80.6 \pm 0.1\%$ ,  $p < 0.001$ ) or progesterone ( $81.5 \pm 0.3\%$ ,  $p < 0.05$ ). There was also a significant reduction in blood-brain barrier permeability to  $\alpha$ -aminoisobutyric acid in normal brain following either treatment (e.g.,  $2.21 \pm 0.19$  and  $1.37 \pm 0.10$   $\mu\text{l/g/min}$ ,  $p < 0.001$ , for control and dexamethasone treatments, respectively), but no effect on the permeability to sodium (e.g.,  $1.19 \pm 0.05$  and  $1.12 \pm 0.11$   $\mu\text{l/g/min}$  for control and dexamethasone treatments, respectively). Furthermore, steroid treatment did not reduce blood-brain barrier permeability to sodium in ischemic brain (e.g.,  $2.53 \pm 0.39$  and  $2.40 \pm 0.33$   $\mu\text{l/g/min}$  for control and dexamethasone treatments, respectively). We conclude that pretreatment with dexamethasone and, to a lesser extent, progesterone reduces brain edema during the early stages of ischemia; however, this effect is not the result of reduced blood-to-brain sodium transport. (*Stroke* 1990;21:1199-1204)

**D**espite the fact that corticosteroids have been used clinically to treat brain edema for three decades, the mechanism of their antiedema effect remains unknown. The efficacy of steroids is most clearly seen in patients with brain tumors; however, these agents are also frequently used to treat brain edema associated with cerebral abscesses, head injury, and stroke. Although steroid therapy has been shown to reduce brain damage or edema in some animal studies of cerebral ischemia,<sup>1-6</sup> other studies have reported no benefit<sup>7-12</sup> and clinical trials show little or no improvement in outcome.<sup>13</sup> Since its mechanism of action is unknown, it is difficult to know whether dexamethasone, the agent most often used, is the most appropriate steroid and whether it has

been administered at the proper time and in the optimal dose.

Dexamethasone reduces permeability of the normal blood-brain barrier (BBB).<sup>14-16</sup> In isolated brain capillaries, high concentrations of steroids inhibit active ion transport mediated by Na,K-ATPase; however, progesterone is 10 times more potent than dexamethasone.<sup>17</sup> Capillary Na,K-ATPase probably plays an important role in BBB sodium transport,<sup>18</sup> and the rate of sodium transport from blood to brain appears to determine the rate of edema accumulation during the early stages of ischemia while the BBB is still intact.<sup>19</sup> Thus, we postulated that steroids reduce the accumulation of brain edema during ischemia by reducing BBB permeability to sodium, either through a direct effect on brain capillary Na,K-ATPase or through a generalized effect on BBB permeability to all compounds. Furthermore, if the mechanism involves a direct effect on sodium transport by brain capillaries, then progesterone might be more efficacious than dexamethasone.

We determined the effect of pretreatment with either dexamethasone or progesterone on the accu-

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mulation of brain edema following focal cerebral ischemia. We also assessed the effect of these treatments on BBB permeability to sodium and  $\alpha$ -aminoisobutyric acid (AIB). The latter compound crosses the BBB by simple diffusion<sup>20</sup> and, therefore, serves as an indicator of the integrity and diffusional permeability of the BBB.

### Materials and Methods

Male Sprague-Dawley rats weighing 280–420 g were subjected to right middle cerebral artery occlusion using the method of Bederson et al.<sup>21</sup> In brief, rats were anesthetized with 50 mg/kg i.m. ketamine hydrochloride and 10 mg/kg i.m. xylazine. An incision was made midway between the right eye and ear, the temporal fascia was incised, and the muscle was separated along the plane of its fibers. The zygoma was cut near its posterior attachment to the skull, and a 10-mm craniectomy was performed. The dura was incised, and the arachnoids adjacent to the middle cerebral artery were removed prior to occlusion. In 61 rats 5–7 mm of the middle cerebral artery was cauterized from the olfactory tract to the rhinal fissure. Body temperature was maintained at  $37 \pm 1^\circ \text{C}$  from the time of anesthesia until the rats were awake. Rats were given food and water ad libitum both before the onset of and after the recovery from anesthesia.

One hour before middle cerebral artery occlusion, rats were given 2 mg/kg i.p. dexamethasone ( $n=22$ ) or progesterone ( $n=17$ ) dissolved in 2% ethanol in sesame oil (0.5 mg steroid/ml). Control rats ( $n=22$ ) received a similar volume of vehicle. Approximately 3.5 hours after middle cerebral artery occlusion, rats were anesthetized again with ketamine and xylazine. Catheters were placed in the femoral vein for administration of isotope and in the femoral arteries for monitoring of blood pressure, blood gases, hematocrit, plasma osmolality, blood glucose concentration, and radioisotope content. Rats were decapitated 4 hours after middle cerebral artery occlusion. The brains were quickly removed, the hemispheres were divided, and the subcortical structures were removed. The remaining cortical shells from the ischemic and nonischemic hemispheres were placed flat and then divided into three samples using 7- and 10-mm cork borers (Figure 1). The center zone was taken from the lateral cortex directly underlying the initial (occluded) portion of the middle cerebral artery. The intermediate zone was a ring of tissue surrounding the center, while the outer zone consisted of the remaining cortical tissue. The location of these samples was chosen to represent the center, intermediate, and outer zones of the ischemic tissue.

For determination of water and ion contents, the brain samples were placed in preweighed crucibles, weighed, dried for 24 hours at  $100^\circ \text{C}$ , and then weighed again. Percentage water of the brain tissue was calculated as the difference between the wet and dry weights. Dried brain samples were subsequently ashed in a muffle oven at  $400^\circ \text{C}$  for 16 hours. The residues were dissolved in 7 ml water, and sodium

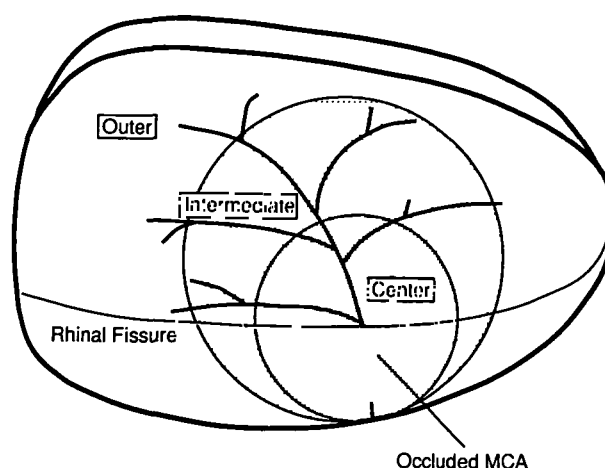


FIGURE 1. Schematic diagram showing occluded middle cerebral artery (MCA) and locations of three tissue samples representing center, intermediate, and outer ischemic zones.

and potassium contents were determined by flame photometry with cesium as the internal standard.

Permeability of the BBB to sodium-22 and [ $^3\text{H}$ ]AIB was determined by a modification of the method of Ohno et al.,<sup>22</sup> in which the integral of radioactivity in the arterial blood was measured by continuous withdrawal at a constant rate.<sup>23</sup> A mixture of 35  $\mu\text{Ci}$  [ $^3\text{H}$ ]AIB and 15  $\mu\text{Ci}$  sodium-22 in 0.2 ml saline was injected and allowed to circulate for 10 minutes. At the end of the experiment, a terminal plasma sample was obtained, the brain was removed, and the ischemic and nonischemic cortices were divided into the three samples described above. Results are expressed as a rate constant for brain uptake, which represents the product of capillary permeability to the tracers ( $P$ ) and surface area of the exposed vascular bed ( $S$ ). This  $PS$  product was calculated as  $C_{ev}/\int C_a dt$ , where  $C_{ev}$  is the concentration of extravascular tracer in brain and  $\int C_a dt$  is the integral of the arterial tracer concentration. Total tracer counts in the brain samples ( $C_{br}$ ), final tracer concentration in the plasma ( $C_p$ ), and plasma volume of the brain sample ( $PV$ ) were used to calculate  $C_{ev}$  as  $C_{br} - (C_p \times PV)$ .  $PV$  was estimated in separate groups of control or dexamethasone-treated rats by determining the [ $^3\text{H}$ ]inulin content of brain and plasma 3 minutes after injecting 50  $\mu\text{Ci}$  of the tracer.

All data are reported as mean  $\pm$  SEM. Differences between control and steroid-treated groups were identified using analysis of variance, and the level of significance of treatment groups compared with the control group was determined using Student's  $t$  test for unpaired samples with Bonferroni's correction for multiple comparisons.<sup>24</sup> Samples from ischemic and nonischemic hemispheres within the same treatment group were compared using Student's  $t$  test for paired samples.

Sprague-Dawley rats were obtained from Charles River, Portage, Mich. Sodium-22, [ $^3\text{H}$ ]AIB (methyl- $^3\text{H}$ ), methoxy-inulin (methoxy- $^3\text{H}$ ), and Protosol

**TABLE 1. Physiological Parameters During Last Half Hour of Middle Cerebral Artery Occlusion in Rats**

Parameter	Control (n=22)	Dexa- methasone (n=22)	Proges- terone (n=17)
Body weight (g)	342±10	336±8	340±9
Mean blood pressure (mm Hg)	111±3	113±3	104±4
Body temperature (°C)	37.2±0.1	37.1±0.1	37±0.2
Arterial pH	7.40±0.01	7.39±0.01	7.40±0.01
Paco <sub>2</sub> (mm Hg)	41±1	41±1	40±1
Pao <sub>2</sub> (mm Hg)	78±2	72±1*	80±2
Hematocrit	0.47±0.01	0.48±0.01	0.47±0.01
Plasma osmolality (mosm)	293±2	294±2	293±2
Blood glucose (mg %)	229±5	255±7†	219±10

Values are mean±SEM.

\*†*p*<0.05, 0.01, respectively, different from control using analysis of variance and two-tailed *t* tests with Bonferroni's correction for multiple comparisons.

were produced by Du Pont–New England Nuclear, Boston, Mass. Steroids and other chemicals were purchased from Sigma Chemical Co., St. Louis, Mo.

### Results

Values for the physiological parameters obtained during the last half hour from all rats in the three groups are given in Table 1. There were no significant differences between the progesterone-treated and control groups; however, Pao<sub>2</sub> and blood glucose concentration were different in the dexamethasone-treated group. The difference in Pao<sub>2</sub> was small and unlikely to have had a significant effect on the results, while the increase in blood glucose concentration was expected given the hyperglycemic effect of glucocorticoids.

Tissue water and ion contents are given in Table 2. Both the ischemic and nonischemic cerebral cortices were divided into three samples. As reported in our previous study,<sup>25</sup> the average cerebral blood flow after 4 hours of ischemia is approximately 17, 26, and 44 ml/100 g/min in the center, intermediate, and outer zones, respectively, of the ischemic cortex compared with 82, 72, and 67 ml/100 g/min in the nonischemic tissue. This gradation in severity of ischemia resulted in a similar gradation in the amount of edema as shown by differences in water content between the ischemic and nonischemic hemispheres in all groups (Table 2). However, while there were still significant differences between the ischemic and nonischemic cortices in the dexamethasone- and progesterone-treated groups, water content of the ischemic tissue was generally less than control in these groups. This difference was significant in the center zone, where edema was reduced by 38% in the dexamethasone-treated group and by 16% in the progesterone-treated group. Steroid therapy had no effect on water content of the nonischemic brain tissue.

The accumulation of brain edema was accompanied by an increase in total brain sodium and a decrease in brain potassium that were proportional to the change in brain water content (Table 2). Treatment with either dexamethasone or progesterone reduced the magnitude of these ionic shifts by approximately the same degree as they reduced brain edema. These results suggest that treatment with either dexamethasone or progesterone significantly reduces the appearance of the cytotoxic or intact-barrier<sup>26</sup> type of edema that is seen during the early stages of ischemia and that is associated primarily with the influx of ions from blood to brain.

Brain inulin spaces were determined only in control and dexamethasone-treated rats (Table 3). There were no differences between these groups and, there-

**TABLE 2. Brain Water and Ion Contents 4 Hours After Middle Cerebral Artery Occlusion in Rats**

Zone	Control			Dexamethasone			Progesterone		
	Nonischemic	Ischemic	<i>p</i> *	Nonischemic	Ischemic	<i>p</i> *	Nonischemic	Ischemic	<i>p</i> *
Water content (%)									
Center	78.7±0.2	82.4±0.2	<0.0001	78.3±0.2	80.6±0.1†	<0.0001	78.4±0.2	81.5±0.3‡	<0.0001
Intermediate	78.5±0.2	80.0±0.3	<0.002	78.2±0.3	79.1±0.2	<0.002	78.2±0.1	80.0±0.3	<0.005
Outer	79.2±0.1	79.9±0.3	<0.025	78.8±0.2	79.2±0.3	<0.025	78.9±0.3	79.5±0.2	<0.02
Sodium content (meq/kg dry wt)									
Center	215±6	528±27	<0.0001	213±6	385±14†	<0.0001	206±6	450±26‡	<0.0001
Intermediate	223±7	299±12	<0.002	224±3	265±13	<0.02	196±17	269±18	<0.005
Outer	241±8	260±15	NS	233±12	243±7	NS	227±5	246±17	NS
Potassium content (meq/kg dry wt)									
Center	482±9	262±11	<0.0001	476±12	364±20†	<0.0001	463±9	300±23	<0.0001
Intermediate	497±14	429±14	<0.01	483±12	453±20	NS	431±35	428±12	NS
Outer	540±16	485±16	NS	511±16	482±18	NS	488±7‡	516±32	NS

Values are mean±SEM, 6–7 rats in each group.

\*Level of significance for differences between ischemic and nonischemic hemispheres using paired, one-tailed *t* test. NS, not significant.

†‡*p*<0.001, 0.05, respectively, different from control using analysis of variance and one-tailed *t* tests with Bonferroni's correction for multiple comparisons.

**TABLE 3. Inulin Space 4 Hours After Middle Cerebral Artery Occlusion in Rats**

Zone	Control		Dexamethasone	
	Nonischemic	Ischemic	Nonischemic	Ischemic
Center	8.27±0.63	8.14±0.5	9.16±0.30	10.15±0.69
Intermediate	8.80±0.54	8.31±0.62	9.61±0.44	9.61±0.46
Outer	10.34±0.61	10.36±0.76	11.33±1.07	9.89±0.25

Values are mean±SEM, 7 rats in each group. There were no significant differences within or between groups.

fore, an average of their values was used to represent the plasma volume of the progesterone-treated rats.

The BBB permeabilities, expressed as the PS product, for AIB and sodium are shown in Table 4. Since AIB enters the brain by simple diffusion,<sup>20</sup> the PS product for AIB is a measure of the passive permeability of the BBB. In the control group, the PS product for AIB did not differ between the ischemic and nonischemic tissue in the center and outer zones but was significantly decreased in the ischemic tissue of the intermediate zone. This result indicates that the integrity of the BBB is maintained during the first 4 hours of ischemia in this model and confirms that the edema is an intact-barrier type. In contrast, the PS product for sodium was significantly increased in the ischemic tissue of the center and outer zones but did not differ in the intermediate zone. This relative stimulation of BBB sodium transport in ischemic brain has been noted previously.<sup>27-29</sup>

Treatment with dexamethasone and, to a lesser extent, progesterone decreased BBB permeability to AIB in the nonischemic tissue (Table 4). The magnitude of this reduction for dexamethasone (37–46%) is very similar to that reported in a previous study using both AIB and sucrose to measure BBB permeability.<sup>16</sup> This steroid effect is also apparent in the ischemic tissue (30–39% reduction), but due to the greater variability of the PS products in the ischemic tissue of the center zone, the difference is significant only in the intermediate and outer zones. In contrast, steroid therapy had no effect on BBB permeability to sodium in either the ischemic or the

nonischemic cortex (Table 4). Thus, the reduction in brain edema that results from steroid treatment cannot be explained by an effect on blood-to-brain sodium transport.

### Discussion

In a previous study, we suggested that the accumulation of brain edema during the early stages of incomplete ischemia is limited by the rate at which sodium enters brain from blood.<sup>19</sup> This proposal was based on two observations. First, the appearance of edema within the tissue is entirely accounted for by the change in total brain cations. Since brain sodium content increases during ischemia while the potassium content decreases, the net increase in brain cations is the result of a gain of brain sodium in excess of the loss of brain potassium. Second, the rate at which total brain sodium content increases is the same as the rate of unidirectional transport of sodium from blood to brain. Thus, all of the sodium that crosses the BBB appears to stay in the tissue, and the extent to which its accumulation exceeds the loss of tissue potassium determines how much edema accumulates. If brain sodium uptake is indeed rate-limiting for brain edema accumulation, then reducing BBB sodium transport should reduce brain edema.<sup>29</sup> Since Na,K-ATPase in the brain capillary endothelium is probably the major driving force for BBB sodium transport<sup>18</sup> and since steroids inhibit Na,K-ATPase activity in isolated brain capillaries,<sup>17</sup> dexamethasone could be a useful compound for examining the relation between BBB sodium transport and ischemic edema accumulation.

This study was designed to test the hypothesis that steroids reduce ischemic brain edema by inhibiting blood-to-brain sodium transport. Furthermore, we predicted that progesterone would have a greater effect on brain edema and the PS product for sodium than dexamethasone because progesterone is a more potent inhibitor of capillary Na,K-ATPase.<sup>17</sup> We found that a high, single dose of either dexamethasone or progesterone significantly reduced the intact-

**TABLE 4. PS Products for  $\alpha$ -Aminoisobutyric Acid and Sodium 4 Hours After Middle Cerebral Artery Occlusion in Rats**

Zone	Control			Dexamethasone			Progesterone		
	Nonischemic	Ischemic	<i>p</i> *	Nonischemic	Ischemic	<i>p</i> *	Nonischemic	Ischemic	<i>p</i> *
<b><math>\alpha</math>-Aminoisobutyric acid</b>									
Center	2.21±0.19	2.20±0.14	NS	1.37±0.10†	1.81±0.24	NS	1.42±0.14‡	1.59±0.16	NS
Intermediate	3.14±0.33	1.96±0.19	<0.005	1.70±0.16†	1.31±0.10‡	<0.01	2.09±0.30§	1.46±0.14§	<0.05
Outer	2.70±0.19	2.63±0.21	NS	1.69±0.17‡	1.60±0.14†	NS	1.96±0.19†	1.84±0.1‡	NS
<b>Sodium</b>									
Center	1.19±0.05	2.53±0.39	<0.001	1.12±0.11	2.40±0.33	<0.01	1.18±0.11	2.54±0.40	<0.01
Intermediate	2.92±0.14	2.64±0.21	NS	2.65±0.21	2.54±0.16	NS	2.51±0.22	2.79±0.22	NS
Outer	2.22±0.10	2.77±0.11	<0.005	2.05±0.14	2.27±0.14	NS	1.99±0.19	2.69±0.26	<0.005

Values, in  $\mu$ l/g/min, are mean±SEM, 8–10 rats in each group.

\*Level of significance for differences between ischemic and nonischemic hemispheres using paired, two-tailed *t* test. NS, not significant.

†‡§p<0.001, 0.01, 0.05, respectively, different from control using analysis of variance and one-tailed *t* tests with Bonferroni's correction for multiple comparisons.



barrier edema seen early during ischemia; however, dexamethasone was more potent than progesterone. Furthermore, the reduction in brain edema was seen without a significant reduction in the PS product for sodium, a measure of the rate of unidirectional sodium transport from blood to brain. Thus, we must reject our hypothesis that steroids reduce ischemic brain edema by inhibiting BBB sodium transport. However, the diffusional permeability of the BBB as measured by the PS product for AIB was significantly reduced by both dexamethasone and progesterone. This reduction was similar in magnitude to the steroid effects on brain edema and net cation changes.

Several aspects of our results require further consideration. The lower efficacy of progesterone compared with dexamethasone might be explained by a lower delivery of progesterone to brain. This is unlikely, however, since progesterone has the highest BBB permeability among naturally occurring steroids.<sup>30</sup> The fact that progesterone has any effect at all on ischemic brain edema and BBB permeability suggests that its effect is not mediated through corticosteroid receptors since progesterone has a negligible interaction with these receptors.<sup>31</sup> Induction of the synthesis of proteins such as lipocortin<sup>32</sup> is probably also not involved since the effect on brain edema is readily apparent within 5 hours and the PS product responds within 3 hours<sup>6</sup> after dexamethasone administration. However, an immediate effect related to the steroid-induced release of stored lipocortin<sup>32</sup> cannot be ruled out. Thus, the effect of dexamethasone on BBB permeability and ischemic brain edema may result from a nonspecific interaction of steroids with cell membranes or other cellular constituents.

The BBB permeability to AIB did not increase in ischemic tissue. This suggests that the BBB had not broken down and that the edema was of the intact-barrier type.<sup>26</sup> However, since changes in P and S cannot be distinguished in the calculation of a PS product, we cannot rule out the possibility that an increase in P was exactly offset by a decrease in S. The same difficulty exists for sodium. However, when the two isotopes are injected and allowed to circulate simultaneously, they should be exposed to the same surface area, and consequently, the ratio of their PS products should represent the ratio of their permeabilities. If this ratio changes, then the permeability of one compound is affected differently from that of the other.

We observed effects of both dexamethasone and progesterone on the PS product for AIB but not on that for sodium in nonischemic brain. This suggests that either 1) the P for AIB is decreased relative to that for sodium or 2) the P for sodium is selectively increased while the S for both compounds is decreased. We believe that the former possibility is more likely since we do not know of any mechanism that will lead to a persistent decrease in perfused capillary surface in normal brain. Although capillary recruitment can change PS products, the effect is apparent only with

short tracer circulation times (<3 minutes) (R.F. Keep, S.R. Ennis, A.L. Betz, unpublished observations). In ischemic brain, a decrease in the capillary surface area could result from a decrease in the number of perfused capillaries as observed previously during incomplete ischemia in gerbils.<sup>27</sup>

The selective change in AIB permeability in response to steroid treatment suggests that AIB and sodium enter the brain by different mechanisms. This is consistent with the view that AIB crosses the BBB by simple diffusion<sup>20</sup> while sodium depends on carrier-mediated transport systems.<sup>18</sup> Further support for different mechanisms of brain uptake is found in the stimulation of sodium permeability with no change in AIB permeability in ischemic tissue. We have previously observed this same differential effect on sodium permeability in rats subjected to middle cerebral artery occlusion<sup>28</sup> and in gerbils subjected to unilateral ischemia and reperfusion.<sup>27</sup> Similarly, Shigeno et al<sup>29</sup> observed a stimulation in brain sodium uptake during focal cerebral ischemia in cats. We speculate that sodium transport is stimulated by the large increase in potassium concentration in the interstitial fluid of ischemic brain.

How is it that steroids reduce brain edema and cation accumulation in ischemic brain without changing blood-to-brain sodium transport? Perhaps the steroid effect results from an interaction of steroids with neuronal or glial cells, resulting in improved ion homeostasis during ischemia. For example, dexamethasone and progesterone may function as free radical scavengers<sup>33–35</sup> that improve cellular viability and reduce edema as do other free radical scavengers.<sup>25,36</sup> Alternatively, steroids might reduce ischemic brain damage by improving blood flow to the tissue. However, neither possibility explains why the effects of dexamethasone and progesterone on edema accumulation in ischemic brain are similar to their effects on the passive permeability of the BBB in normal brain. It is possible that steroids reduce ischemic brain edema by reducing BBB permeability to a solute other than sodium that crosses the BBB by simple diffusion and the brain uptake of which is rate-limiting for edema accumulation. The chloride ion is a good candidate for this solute because it is known to accumulate in ischemic brain in parallel with edema formation.<sup>37</sup> Further investigation will be required to determine which, if any, of the above mechanisms explains the efficacy of steroids in the treatment of ischemic brain edema.

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