Polyethylene Glycol Superoxide Dismutase and Catalase Attenuate Increased Blood–Brain Barrier Permeability After Ischemia in Piglets

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Background and Purpose: Transport of urea across the blood–brain barrier is increased during postischemic cerebral reperfusion in the piglet. Ischemia/reperfusion also has been observed to increase apparent superoxide anion generation on the surface of the brain. The present study was designed to address the hypothesis that the increased transfer of urea into the brain after ischemia/reperfusion could be due to superoxide anion–induced alterations in blood–brain barrier permeability.

Methods: Blood-to-brain transfer of carbon-14-labeled urea was measured in four groups (n=7 each) of newborn pigs: 1) control (no ischemia, no pretreatment), 2) pretreatment with polyethylene glycol superoxide dismutase (1,000 IU/kg) and polyethylene glycol catalase (10,000 IU/kg i.v.) but no ischemia, 3) no pretreatment and 20 minutes of ischemia followed by 2 hours of reperfusion, and 4) pretreatment with polyethylene glycol superoxide dismutase and polyethylene glycol catalase in addition to ischemia/reperfusion. The following brain regions were investigated: cerebrum, caudate, midbrain, pons, medulla, and cerebellum.

Results: Polyethylene glycol superoxide dismutase inhibited generation of superoxide anion by the brain during reperfusion after ischemia. Regional transfer of [14C]urea from blood to brain increased at 2 hours' reperfusion. This ischemia-induced increase in blood-to-brain transfer of [14C]urea was attenuated by pretreatment with polyethylene glycol superoxide dismutase and polyethylene glycol catalase: e.g., cerebrum Kuv was 28±2 in the control group, 26±3 in the pretreated/no ischemia group, 67±5 in the untreated/ischemia group, and 40±2 ml·g⁻¹·s⁻¹·10⁻⁶ in the pretreated/ischemia group. After ischemia/reperfusion, cerebral blood flow was unchanged by pretreatment with polyethylene glycol superoxide dismutase and polyethylene glycol catalase.

Conclusions: These data suggest that production of a partially reduced species of oxygen contributes to the increased urea transfer across the blood–brain barrier after ischemia in the newborn pig. (Stroke 1992;23:755–762)

Key Words • blood–brain barrier • cerebral circulation • cerebral ischemia • infant

Ischemia/reperfusion injury results in altered cerebral hemodynamics and blood–brain barrier permeability. In piglets, ischemia/reperfusion produces an initial hyperemia followed by a reduction in cerebral blood flow in most brain regions except the cerebrum, where the hyperemia is far less in magnitude.† Cerebral vascular responsiveness is also affected by ischemia/reperfusion. For example, there is a selective loss of prostanoid-dependent pial arteriolar vasodi-
University of Tennessee, Memphis. Newborn pigs (1-3.2 kg, 1-5 days old) of either sex were anesthetized with halothane-nitrous oxide and ventilated with supplemental oxygen using a positive-pressure infant respirator after intubation with a 3-mm endotracheal tube. Body temperature was maintained at 37-38°C with an overhead radiant warmer. Catheters were placed in both femoral arteries and femoral veins.

The piglets were divided into four groups. These groups were as follows: 1) control group (no ischemia; received 5 ml saline as vehicle), 2) pretreated/no ischemia group (received 1,000 IU/kg polyethylene glycol superoxide dismutase [PEG-SOD] and 10,000 IU/kg polyethylene glycol catalase [PEG-CAT; Sigma Chemical Co., St. Louis, Mo.]), 3) untreated/ischemia group (no pretreatment and 20 minutes of ischemia followed by 2 hours of reperfusion), and 4) pretreated/ischemia group (received 1,000 IU/kg PEG-SOD and 10,000 IU/kg PEG-CAT, then underwent 20 minutes of ischemia followed by 2 hours of reperfusion). Treatment animals received PEG-SOD and PEG-CAT 30 minutes before ischemia.

Cerebral ischemia was produced with a hollow brass bolt that was implanted in the left parietal cranium as described previously in detail. An incision was made in the scalp, and a 3-mm hole was drilled using a hollow toothless bit. With the dura intact, a threaded bolt was placed in the hole to a depth flush with the inner skull surface. Total brain ischemia was produced by reducing the cerebral perfusion pressure to zero for 20 minutes. Artificial cerebrospinal fluid was infused through the bolt to raise intracranial pressure (measured at the bolt via a side-arm manometer) to 15 mm Hg greater than mean arterial blood pressure. To prevent the arterial blood pressure from rising inordinately (Cushing response), blood was withdrawn as necessary to maintain mean arterial blood pressure no higher than 100 mm Hg. As the Cushing response subsided, the withdrawn blood (anticoagulated with citrate and dextrose) was reinfused. At the end of the ischemia period, the bolt was opened to atmospheric pressure, allowing intracranial pressure to fall rapidly. The bolt was sealed with bone wax, and a period of 2 hours of reperfusion followed. We have previously shown that this method of brain ischemia results in no blood flow to any brain region during the ischemic period. Control animals were ventilated for 2 hours before measurement of tracer transport.

Superoxide dismutase-inhibitable nitroblue tetrazolium (NBT) reduction as an index of apparent cerebral superoxide anion generation was measured during reperfusion after total cerebral ischemia using dual cranial windows in four additional piglets pretreated with PEG-SOD. We have previously shown that sufficient superoxide anion radicals are produced by newborn pig brain to reduce 8.7±1.5 pmol NBT/mm² in 20 minutes during posts ischemic reperfusion. Briefly, SOD-inhibitable NBT reduction was determined by placing NBT (Sigma, 2.4 mM) dissolved in cerebrospinal fluid under the window and NBT (2.4 mM) and SOD (Sigma, 60 units/ml) in cerebrospinal fluid under the other. Nitroblue tetrazolium is water soluble and forms a yellow solution that is converted to nitroblue formazan, an insoluble purple precipitate, in the presence of reducing agents. The SOD-inhibitable NBT reduction was determined by the differences in quantities of nitroblue formazan precipitated on the brain surface under the two windows. Although NBT can be reduced by a variety of agents, SOD provides specificity for the assay.

To determine the amount of the precipitated nitroblue formazan, 1-mm-thick slices of the brain surface under each cranial window were removed. The slices were minced and homogenized in 1N NaOH and 0.1% sodium dodecyl sulfate. The mixture was centrifuged at 20,000g for 20 minutes, the resulting supernatant discarded, and the pellet resuspended in 3 ml pyridine. Because nitroblue formazan cannot be measured in the presence of hemoglobin, we extracted hemoglobin before dissolving the nitroblue formazan in pyridine. Thus, when tissues were digested with lye and detergent, the freed hemoglobin dissolved in the aqueous solution, and the insoluble formazan could be removed by centrifugation. The nitroblue formazan was then dissolved in the pyridine during heating at 80°C for 1 hour. Particulate matter was removed by a second centrifugation at 10,000g for 10 minutes. The concentration of nitroblue formazan in the resulting solution was determined spectrophotometrically at 515 nm. The nitroblue formazan on the NBT-only side was read against the background of the SOD-treated side. Calibration solutions were prepared freshly and treated identically to the samples.

Catheters were placed in both femoral arteries and femoral veins. One set of catheters was used to monitor blood pressure, sample arterial blood, and provide venous access as necessary. The other set of femoral catheters was connected with a 5-cm length of silicon tubing to form an arteriovenous shunt. This shunt allowed for rapid, multiple sampling of arterial blood. Heparin (50 units/kg) was given intravenously to maintain shunt patency.

Calculation of the $K_{as}$ transfer constant ($cm^{-1}\cdot g^{-1}\cdot s^{-1}\times10^6$) into the brain used the following equation previously described by Ohno et al:

$$K_{in} = \frac{\int_0^T (C_t - C_b) dt}{\int_0^T C_p dt}$$

where $C_t$ (T) is the tracer concentration in the brain tissue (disintegrations per minute per gram) at the end of the experiment, $C_b$ is the tracer concentration in the residual blood (disintegrations per minute per gram) at the end of the experiment, $C_p$ is the tracer concentration in plasma (disintegrations per minute per milliliter), and $T$ is the time of uptake when brain tracer content is determined. Calculation of the $K_{as}$ transfer constant yields a number that reflects the permeability of a substance in a two-compartment system, with one compartment being the plasma and the second the brain. Following its intravenous injection, the tracer disappears from the plasma into the extravascular spaces. Therefore, the tracer plasma concentration ($C_p$) is time dependent. The values for the brain tracer concentration [$C_t (T)$] and the residual plasma tracer concentration ($C_b$) are obtained experimentally.
At 2 hours of reperfusion, 50 μCi of carbon-14-labeled urea (New England Nuclear, Boston, Mass.) was injected as an intravenous bolus. Blood samples were taken from the arteriovenous shunt at 0, 5, 10, 15, 20, 30, 40, 50, 60, 70, 90, 180, 240, 360, 480, 600, 900, and 1,200 seconds (0.08, 0.16, 0.25, 0.33, 0.50, 0.67, 0.83, 1.0, 1.17, 1.5, 3, 4, 6, 8, 10, 15, and 20 minutes). The piglet was then killed, the head elevated 10 cm above the heart, and the brain rapidly removed. The brain was washed with normal saline, dissected into major regions, and weighed. Brain tissues were homogenized in 10 ml IN NaOH and 0.1% sodium dodecyl sulfate, from which the uppermost 5 ml was centrifuged for 20 minutes at 20,000g. In a subset of the four experimental groups, regional cerebral blood flow (radio-diolabeled microspheres; see below) and the transport of [14C]urea were determined in the same animals. In these experiments, the uppermost 5 ml of the supernatant was added to 8 ml scintillation fluid because the microspheres were on the bottom. Blood samples (300,000–800,000 microspheres) were injected into the left ventricle, and the injection line was flushed with 1 ml saline. Withdrawal of reference blood sample was begun 15 seconds before microsphere injection and continued for 2 minutes after the injection. After the experiment, the brain was removed for determination of radioactivity. Preliminary experiments showed that the radioactive microspheres remained entirely with the tissue precipitant from the above centrifugation. Blood flow to each tissue at the time the microspheres were injected was calculated from the formula Q = C • R • CR −1, where Q is organ blood flow (in milliliters per minute per 100 g), C is counts per 100 g tissue, R is rate of withdrawal of reference arterial blood sample (in milliliters per minute), and CR is total counts in reference arterial blood sample.

To examine microvascular ultrastructure, closed cranial windows were surgically implanted (see above). Animals were divided into three groups: 1) control (no ischemia), 2) untreated/ischemia (20 minutes, followed by 45 minutes of reperfusion), and 3) pretreated/ischemia (treated with PEG-SOD [see above], followed by 20 minutes of ischemia, then 45 minutes of reperfusion). At the end of the protocol, the cortical surface was covered with 2% aqueous gluteraldehyde. Ten minutes later, the pia, arachnoid, and surface vessels were peeled away and diced in 2% gluteraldehyde. Routine thick cuts (1.0–1.4 μm) were stained by toluidine blue for survey before thin cuts (0.4 μm) and lead citrate staining for electron microscopy using a Zeiss 10C.

Values are presented as mean±SEM. Comparisons among groups were made using analysis of variance with a Scheffe post hoc test. A significance level of p<0.05 was used.

**Results**

Mean arterial blood pressure, arterial blood gases, and pH were determined at the beginning and at the end of each experiment (Table 1). There were no significant differences in any of these parameters during the measurement periods described in this report. Pretreatment of piglets with PEG-SOD completely blocked the increase in SOD-inhibitable NBT reduction during postischemic reperfusion. None of the four piglets pretreated with PEG-SOD had detectable SOD-inhibitable NBT reduction during reperfusion after ischemia. The minimum amount of NBT detectable is 1 pmol/mm² during 20 minutes of reperfusion. The undetectable SOD-inhibitable NBT reduction in PEG-SOD-treated piglets after ischemia is in contrast to 8.7±1.5 pmol/mm² during 20 minutes of reperfusion in untreated piglets.²

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<th>PaO₂ (mm Hg)</th>
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Values are mean±SEM; n=7 piglets for each group. MAP, mean arterial pressure; pretreated, given 1,000 IU/kg polyethylene glycol superoxide dismutase and 10,000 IU/kg polyethylene glycol catalase; ischemia, subjected to 20 minutes of ischemia followed by 2 hours of reperfusion.
FIGURE 1. Transfer constant ($K_a$) (ml·g$^{-1}$·s$^{-1}$·10$^6$) for carbon-14-labeled [$^{14}$C] urea into major regions of the brain in control, SOD-CAT pretreated, ischemia, and ischemia/SOD-CAT pretreated piglets (n=7 for each group). SOD-CAT, treated with polyethylene glycol superoxide dismutase (PEG-SOD) and polyethylene glycol catalase (PEG-CAT); ISC/REP, ischemia/reperfusion. Values are mean±SEM; *p<0.05 compared with control; +p<0.05 compared with ischemia/reperfusion.

[$^{14}$C] urea transport is shown in Figure 1. Transport of [$^{14}$C] urea in the SOD-CAT-no ischemia group was similar to values obtained from animals that received vehicle (Figure 1). Transport of [$^{14}$C] urea into the brain was significantly increased in all brain regions in the ischemia group. However, the elevated transport of [$^{14}$C] urea during ischemia was blunted by pretreatment with PEG-SOD and PEG-CAT (Figure 1).

Regional blood flow was unchanged by the administration of PEG-SOD and PEG-CAT before ischemia (Table 2). Further, there was no difference in regional cerebral blood flow during reperfusion after ischemia between animals that received vehicle and those that received PEG-SOD and PEG-CAT (Table 2).

After cerebral ischemia, ultrastructural alterations of the microvascular endothelium were observed compared with tissue obtained from a control animal (Figures 2 and 3). These included more numerous cytoplasmic inclusions and areas of injured mitochondria (Figures 2 and 3). The irregular luminal surface and cytoplasmic vesicles suggest increased pinocytotic activity. The microvascular endothelium from a PEG-SOD-treated animal had fewer pinocytotic vesicles, and the mitochondria were uninjured, but luminal pockets causing an irregular appearance were still present (Figure 4). Tight junctions were unaffected in all groups (Figures 2–4).

**Discussion**

Results of the present study show that activated oxygen generation contributes to increased transfer of urea from blood to the brain after ischemia/reperfusion because pretreatment with PEG-SOD and PEG-CAT attenuates the transfer of urea into the brain. PEG-SOD and PEG-CAT do not alter K$_a$ values for urea in piglets not exposed to ischemia. These experiments complement our earlier study by providing one possible mechanism for the increased blood-to-brain transfer of urea.

The present study also shows that SOD-inhibitable NBT reduction was not detectable after 20 minutes of reperfusion following ischemia in the PEG-SOD–pretreated animals, indicating that PEG-SOD at the dosage used prevented the formation of superoxide anions. In contrast, we have previously observed that piglets in

<table>
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<th>Group</th>
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<th>Caudate</th>
<th>Midbrain</th>
<th>Pons</th>
<th>Medulla</th>
<th>Cerebellum</th>
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</table>

Values are mean±SEM; n=3 piglets for each group. PEG-SOD, polyethylene glycol superoxide dismutase; PEG-CAT, polyethylene glycol catalase; pretreated, given 1,000 IU/kg PEG-SOD and 10,000 IU/kg PEG-CAT; ischemia, subjected to 20 minutes of ischemia followed by 2 hours of reperfusion.
the untreated/ischemia group produced $8.7 \pm 1.5$ pmol/mm$^2$ NBT during 20 minutes of reperfusion.$^4$

At the ultrastructural level, there were more cytoplasmic inclusions in untreated compared with treated tissues from ischemia/reperfusion piglets. These observations suggest that urea blood-to-brain transfer may involve pinocytosis because tight junctions were unaffected in all groups. There were fewer cytoplasmic vesicles and fewer surface pockets in vessels obtained from PEG-SOD-pretreated animals. The ultrastructural appearance of the endothelium is consistent with decreased pinocytotic activity resulting in reduced alteration of transfer of urea from blood to brain in pretreated ischemia/reperfusion piglets compared with those not pretreated. However, the luminal pockets suggest augmented pinocytosis and are consistent with the increase in urea transport in piglets treated with PEG-SOD and PEG-CAT and subjected to ischemia compared with those not subjected to ischemia. Thus, both functionally and ultrastructurally, pretreatment with PEG-SOD and PEG-CAT appears to attenuate but clearly does not abolish effects of ischemia/reperfusion on the blood–brain barrier.

An increase in cerebral blood flow could cause an apparent increase in permeability if the surface area of exchange is increased. However, we know from previous experiments$^1$ that blood flow and resistance to all areas of the piglet brain except the cerebrum are not different from preischemic levels at 15, 20, 40, and 90 minutes and 24 hours after ischemia. Blood flow to the cerebrum is normal at 15 and 20 minutes, reduced at 40 and 90 minutes, and has returned to control at 24 hours of reperfusion. Therefore, the increased blood-to-brain transfer that we observed during ischemia/reperfusion was not caused by increases in blood flow because no increase in blood flow occurs at any reperfusion time examined. In the present study, regional cerebral blood flow and corresponding changes in blood–brain barrier permeability were determined in the same animal preparation. Blood flow to the cerebrum appeared to be reduced after ischemia, as reported previously.$^1$ Because regional cerebral blood flow was unchanged by PEG-SOD and PEG-CAT, an altered blood flow also cannot account for differences observed between treated and untreated animals during ischemia/reperfusion.

Superoxide and associated activated oxygen species could contribute to changes in cerebral or brain vessel

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**Figure 2.** Transmission electronmicrograph from control piglet showing meningeal vessel with loose bundles of collagen (C) and erythrocytes (R) within the lumen. There are both cavitated mitochondria (m) and a few pinocytotic vesicles (v), less glycogen, and linearly dilated endoplasmic reticulum (E). Note the smooth luminal endothelial surface and paucity of cytoplasmic vesicles. Meningothelial cells have large nuclei (M) compared with endothelial cell nucleus (N). Original magnification, $\times 5,000$; print magnification, $\times 9,780$. 

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endothelium. Superoxide anion appears to be generated through elevated prostaglandin \( \text{H} \) synthase metabolism of arachidonic acid during postischemic reperfusion.\(^4\) Superoxide anion or subsequent activated reduction products can result in altered cerebrovascular endothelium characterized by increased numbers of vacuolar cytoplasmic inclusions, more numerous surface pits, and mitochondrial injury coupled with intravascular neutrophilic granulocyte accumulation.\(^6\) Superoxide anion \( (\text{O}_2^-) \), hydrogen peroxide \( (\text{H}_2\text{O}_2) \), and hydroxyl radical \( (\cdot \text{OH}) \) may be cytotoxic, or free myeloperoxidase released in the extracellular medium may catalyze the oxidation of \( \text{Cl}^- \) by \( \text{H}_2\text{O}_2 \) to yield hypochlorous acid, a potent oxidizing agent.\(^7\) Therefore, it is not unrealistic to propose a link between the increased permeability of the blood–brain barrier and the generation of free radicals. It follows that protection to the brain may be afforded by giving appropriate scavengers during ischemia/reperfusion. Topical superoxide dismutase was effective in a cat model of concussive brain injury in reducing the vasodilation, loss of responsiveness to hypocapnia, and the density of endothelial lesions.\(^8\) Newborn rats with right carotid ligature and hypoxia showed 4% brain swelling ipsilateral to the ligature and 37% increase in the brain volume but no change in cerebral blood flow for up to 24 hours of recovery.\(^9\) Systemic treatment with allopurinol, an inhibitor of xanthine oxidase and scavenger of free radicals, 30 minutes before ligature of the internal carotid and hypoxia protected the brain of the newborn rats, attenuating the cerebral edema and infarction.\(^10\) In sheep, systemic treatment with PEG-SOD (5,000 IU/kg) and PEG-CAT (100,000 IU/kg) prevented the late cerebral hypoperfusion and the late depressed cerebral oxygen metabolism after cerebral asphyxia.\(^11\) Protective effect of scavengers in ischemic/reperfusion injury of other organs has also been observed.\(^12,13\)

Polyethylene glycol–substituted superoxide dismutase and catalase may have a longer plasma life and greater blood–brain barrier penetration than the unsubstituted enzymes. The dose of PEG-SOD chosen was 1,000 IU/kg and the corresponding PEG-CAT dose was 10,000 IU/kg because these are the recommended human doses.\(^14\) Olson et al\(^15\) calculated and measured the activity of PEG-SOD (2,000 IU/kg) and PEG-CAT (10,000 IU/kg) in adolescent pigs and found that the volume of distribution of PEG scavengers was essentially limited to the plasma space, as

**Figure 3.** Transmission electronmicrograph from ischemia/reperfusion piglet showing small vessel interface with the superficial cerebral cortex. We have labeled a large eccentric endothelial nucleus \((N)\) and two vesicles, one an injured mitochondrion \((m)\) and the other pinocytotic \((\cdot v)\). The luminal membrane of endothelium is relatively smooth at places, but in other areas numerous pockets are seen. In contrast to the control endothelium in Figure 2, note the large number of cytoplasmic vesicles and surface pockets. Moderate glycogen is present. There is both mitochondrial injury and swelling of the neuropil beyond the vessel. Original magnification, \( \times 8,000 \); print magnification, \( \times 13,680 \).
PEG-SOD and PEG-CAT are relatively large macromolecules. Nevertheless, extracellular SOD is thought to protect against cellular damage from toxic oxygen species by consuming superoxide anion in the extracellular space, thereby promoting rapid concentration-dependent diffusion of superoxide anion out of the intracellular space. Similarly, we observed that systemic PEG-SOD was able to eliminate the apparent superoxide anion production on the cerebral cortical surface that otherwise accompanies reperfusion after cerebral ischemia. These results suggest that 1,000 IU/kg PEG-SOD administered systemically has sufficient access to the site of superoxide generation to remove the increased superoxide anions generated with ischemia/reperfusion.

In summary, the present study shows that PEG-SOD (1,000 IU/kg) is able to eliminate the increase in SOD-inhibitable NBT reduction on the surface of the brain during reperfusion after ischemia. Pretreatment with PEG-SOD and PEG-CAT partially attenuates the ischemia-induced increase in blood–brain barrier permeability to $[^{14}C]$urea, suggesting that activated oxygen species contribute to the alteration of urea transfer through the blood–brain barrier during reperfusion after cerebral ischemia in the newborn pig.

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Polyethylene glycol superoxide dismutase and catalase attenuate increased blood-brain barrier permeability after ischemia in piglets.
W M Armstead, R Mirro, O P Thelin, M Shibata, S L Zuckerman, D R Shanklin, D W Busija and C W Leffler

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