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Temporary Cerebral Ischemia

Effects of Pentastarch or Albumin on Reperfusion Injury

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Recent investigations have proposed that, after temporary ischemia, pentastarch may reduce microvascular permeability and reperfusion injury. However, this hypothesis has not been tested in the brain. Accordingly, after 180 min of temporary middle cerebral artery occlusion, the effect of pentastarch or albumin on blood–brain barrier permeability and cerebral injury was investigated in isoflurane-anesthetized rats. One of the following was maintained for the final 60 min of occlusion and throughout reperfusion: control-hematocrit was not manipulated; pentastarch-hematocrit was decreased to ≈ 30% with pentastarch; or albumin-hematocrit was decreased (≈ 30%) with albumin. *Part A (n = 21):* 30 min of reperfusion was allowed, and blood–brain barrier permeability was determined with the indicator dye Evans Blue. *Part B (n = 14):* in different animals, 120 min of reperfusion was allowed, and cerebral injury (2,3,5-triphenyltetrazolium chloride stain) and edema (specific gravity) were assessed. *Part C (n = 4):* in different animals, the blood–brain barrier was evaluated by electron microscopy. Evans Blue (micrograms per gram brain tissue, mean ± SD) was greater in the control (20.8 ± 9.0) and albumin (15.5 ± 7.3) groups *versus* the pentastarch (4.7 ± 2.7) group ($P < 0.05$). Brain injury (percent of hemisphere ipsilateral to occlusion) was less and specific gravity greater in the pentastarch (33 ± 8 and 1.040 ± 0.003 respectively) *versus* the albumin group (45 ± 6 and 1.035 ± 0.003). This study supports the hypothesis that during temporary cerebral ischemia, pentastarch decreases brain injury and edema. Electron microscopy did not confirm previous proposals that this effect is mediated by an anatomic sealant action of pentastarch at separated endothelial tight junctions. (Key words: Animals: rat. Brain: injury; ischemia. Hemodilution: albumin; pentastarch.)

A PREDICTABLE CONSEQUENCE of focal cerebral ischemia is damage to the blood–brain barrier (BBB), which may worsen the original injury by exacerbating vasogenic edema.[1] If ischemia is permanent, there is a gradual but steady increase in BBB permeability.[2] However, in the event of cerebral reperfusion, there is a transient but profound increase in BBB permeability that can effect an extensive worsening of brain edema.[3,4] Recent laboratory studies in other organ systems have suggested that hydroxyethyl starch macromolecules (pentastarch) may modify the basement membrane and/or have an anatomic sealant action at separated endothelial junctions, thereby reducing microvascular permeability and reperfusion injury.[5–8] In these studies, an associated effect of pentastarch therapy was hemodilution.

In the setting of focal cerebral ischemia hemodilution therapy has been shown to increase cerebral blood flow, preserve cellular ionic homeostasis, and reduce cerebral injury.[9–12] By improving intravascular rheology, hemodilution is hypothesized to ameliorate ischemia by increasing collateral circulation to, and microcirculatory flow within, an ischemic area of the brain.[11,12] However, during reperfusion (disrupted BBB), increases in microcirculatory flow augment intraluminal hydrostatic pressure, which may worsen vasogenic edema and secondary brain injury.[13]

The purpose of this study was to assess the effects of hemodilution with pentastarch or albumin on vascular permeability, cerebral edema, and injury, after temporary middle cerebral artery occlusion (MCAo) in rats.

Materials and Methods

The study protocol was approved by the institutional Animal Research Committee. Male, spontaneously hypertensive rats (350–400 g, 16–20 weeks old) were fasted with access to water *ad libitum*.

SURGICAL PREPARATION

Each rat was anesthetized with 1.2 MAC isoflurane (1.44%, end-tidal). Following tracheal intubation, the lungs were mechanically ventilated with a Harvard Rodent Respirator (Harvard, Boston, MA). The femoral vessels were cannulated for continuous mean arterial pressure monitoring and maintenance fluid administration (0.9% normal saline at 4 $ml \cdot kg^{-1} \cdot h^{-1}$). Arterial blood (125 μl) was analyzed at 30-min intervals for *p*H, Pa_{CO_2}, Pa_{O_2}, glucose, and hematocrit. Cranial temperature was controlled by servomechanism at 37° C with a heating blanket. The left middle cerebral artery was exposed *via* a subtemporal craniectomy and occluded for 180 min with 10-0 monofilament nylon suture (proximal to the lenticulostriate branch and distal to the inferior cerebral vein). By this means, consistent injury to both cortical and subcortical tissue is achieved.[12,14] Throughout the study period, the craniectomy site was bathed in mock cerebrospinal fluid at 37° C.

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PART A

Following surgical preparation, 21 rats were randomized to one of the following treatments (intravenous), which was instituted at 120 min of MCAo and maintained throughout the remaining 60 min of ischemia and during 30 min of reperfusion.

Control (n = 7): neither hematocrit nor blood volume was manipulated.

Albumin (n = 7): 10-ml · kg^{-1} bolus of 10% albumin (Travenol Laboratories, Glendale, CA) followed by a 10-ml · kg^{-1} · h^{-1} infusion was given to maintain a hematocrit of 29–32%.

Pentastarch (n = 7): a similar volume of pentastarch (Pentaspan®; Du Pont, Wilmington, DE) was administered to maintain a hematocrit of 29–32%.

After 180 min of MCAo, 30 mg · kg^{-1} of Evans Blue dye was given intravenously.[13,15] The sutures were removed and 30 min of reperfusion allowed. Reperfusion was verified by visual inspection of the surgical field. Pilot studies and previous autoradiographic analyses of cerebral blood flow during reperfusion[16] have verified that all brain areas are perfused using this technique.

After 30 min of reperfusion, the descending thoracic aorta was cross-clamped and Evans Blue cleared from the vascular space by aortic perfusion (100 ml of 0.9% NaCl at 37° C). The brains were removed and coronally sectioned 3.0, 5.0, 7.0, and 11.0 mm posterior to the frontal pole (fig. 1). Each brain surface was immediately photographed with color slide film (Ektachrome, tungsten 160 ASA); the film was processed; and the area of Evans Blue extravasation determined with a Drexel/DUMAS image processing system.

Immediately after photography of the brain surfaces, each segment was sagittally divided, weighed, and immersed in formamide (Fisher Scientific, Los Angeles, CA (1 ml · 100 mg^{-1} brain tissue). After 72 h, the optical absorbance of the diluent was determined with a Hitachi 100-80 Computerized Spectrophotometer (San Jose, CA; absorbance wavelength of 620 ηm). The amount of Evans Blue in each hemisphere was calculated from a regression curve derived from Evans Blue/formamide standards. The change in BBB permeability due to MCAo was defined by the difference in Evans Blue between the ischemic and contralateral hemispheres.[13,15]

PART B

Following surgical preparation, 14 different rats were randomly assigned to one of two hemodilution groups as in part A (120 min of ischemia, followed by 60 min of ischemia with hemodilution): pentastarch (n = 7) or albumin (n = 7). However, 120 min (rather than 30 min) of reperfusion was allowed, during which hemodilution was maintained. In Part A the reperfusion period was 30 min, because this is the time period of maximum BBB opening.[13] Conversely, as the purpose in Part B was to measure brain injury and edema, 120 min of reperfusion was allowed (the necessary delay in our model for BBB permeability changes at 0–30 min to manifest brain water differences[12–14,15]). Immediately after the 5-h period of ischemia and reperfusion, the animals were killed by decapitation and the brains removed and coronally sectioned 3.0 mm and 5.0 mm posterior to the frontal pole (fig. 1). The middle brain segment (3.0–5.0 mm posterior to the frontal pole) was immersed in 2% 2,3,5-triphenyltetrazolium chloride (TTC) for 30 min (37° C) to determine the area of ischemic brain injury.[17] Each brain surface was photographed with color slide film and analyzed with a Drexel/DUMAS image-processing system to define the area of deficient TTC staining (fig. 2). All image analysis was performed by an observer who was blinded to study protocol.

The anterior and posterior segments of brain (1.0–3.0 and 5.0–7.0 mm posterior to the frontal pole) were analyzed for brain water content by microgravimetry. A 2.0-mm biopsy punch (Baker and Cummins, Miami, FL) was used to sample matching cortical and basal ganglia areas from both hemispheres (Figure 1). Specific gravity was determined by placing the tissue specimens in a kerosene–bromobenzene density gradient. The linear regression equation of each gradient was determined and verified with potassium sulfate standards.[18]

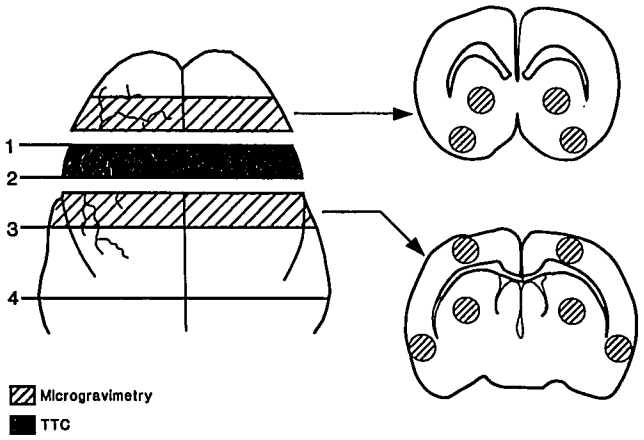

FIG. 1. Method of segmenting the brain for tissue sampling. *Left*: segmenting of brain for analysis of injury (solid), edema (hatched), and Evans Blue (sections 1, 2, 3, and 4). Section 1 = the coronal plane 3.0 mm from the frontal pole; section 2 = 5.0 mm from the frontal pole; section 3 = 7.0 mm from the frontal pole; and Section 4 = 11.0 mm from the frontal pole. *Right*: Specific areas of tissue sampling for microgravimetry.

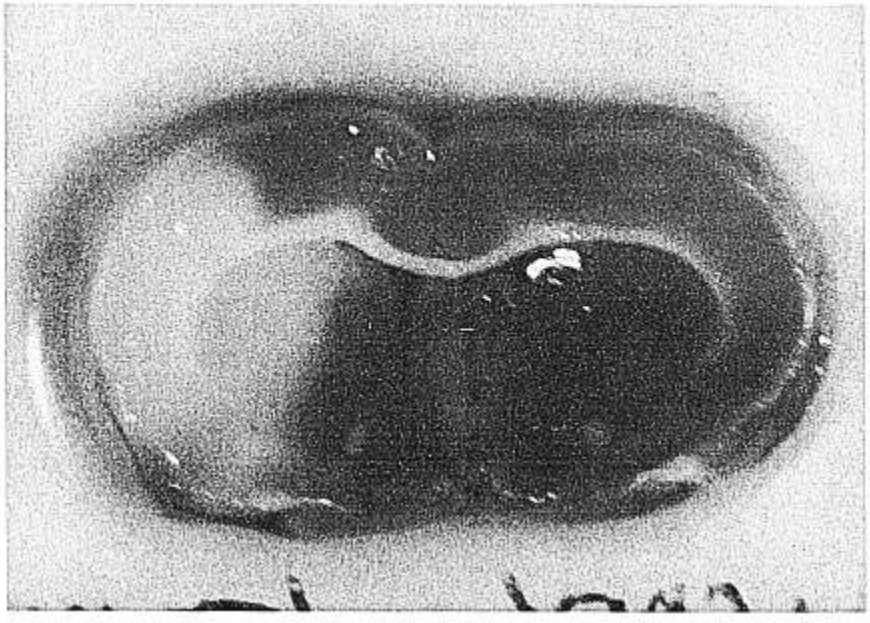

FIG. 2. 2,3,5-triphenyltetrazolium chloride–stained brain section (3.0 mm from the frontal pole). The dark area corresponds to normal brain, and the pale area is defined as injured brain.

PART C

After surgical preparation, four different rats were randomly assigned to one of two hemodilution groups as in part A (120 min of ischemia, followed by 60 min of ischemia with hemodilution and 30 min of reperfusion with hemodilution). After 180 min of ischemia and 30 min of reperfusion, the rats underwent live fixation by perfusion.[13,19] The brain was left for 24 h in the perfusate and then biopsied in the core area of infarct and border zone, and in corresponding areas in the hemisphere contralateral to MCAo. The specimens were postfixed, dehydrated, and embedded in Epon 812. Thick sections (1.0 μm) were cut and stained for light microscopic evaluation and orientation. Thin sections were cut, mounted on one-hole grids, and stained with uranyl acetate and lead citrate.

All intergroup data were evaluated by a two-way analysis of variance, and, as appropriate, mean values were compared by *t* tests with a Bonferroni correction for multiple comparisons.[20] Specific gravity (within a group) was compared between the occluded and nonoccluded hemispheres by a paired *t* test.[20] $P < 0.05$ was considered significant.

Results

All values are reported as mean ± SD. Except for anticipated differences in hematocrit, there were no intergroup differences in the physiologic data (table 1).

PART A

Evans Blue (micrograms per gram brain tissue) was greater in the control (20.8 ± 9.0) and albumin (15.5

TABLE 1. Physiologic Data

	Control	Albumin	Pentastarch
Part A			
*p*H	7.40 ± 0.02	7.41 ± 0.02	7.40 ± 0.02
Pa_{O_2} (mmHg)	145 ± 18	149 ± 22	150 ± 13
Pa_{CO_2} (mmHg)	38.7 ± 1.3	38.8 ± 1.3	39.8 ± 1.1
MAP (mmHg)	144 ± 5	142 ± 8	141 ± 6
Hematocrit-1 (%)	46 ± 3	45 ± 4	46 ± 3
Hematocrit-2 (%)	47 ± 1	31 ± 2*	31 ± 3*
Glucose ($mg \cdot dl^{-1}$)	100 ± 16	107 ± 18	104 ± 14
Part B			
*p*H	—	7.42 ± 0.01	7.41 ± 0.01
Pa_{O_2} (mmHg)	—	139 ± 12	151 ± 19
Pa_{CO_2} (mmHg)	—	38.0 ± 1.4	38.8 ± 1.4
MAP (mmHg)	—	142 ± 7	141 ± 5
Hematocrit-1 (%)	—	45 ± 3	46 ± 3
Hematocrit-2 (%)	—	30 ± 1	31 ± 1
Glucose ($mg \cdot dl^{-1}$)	—	114 ± 9	111 ± 12

Mean ± SD; an average of the 15-min (mean arterial pressure [MAP]) or 30-min (*p*H, Pa_{O_2}, Pa_{CO_2}, hematocrit, and glucose) values during middle cerebral artery occlusion (MCA_O) and reperfusion. In the control group neither hematocrit nor blood volume was manipulated; in the albumin group hematocrit was decreased to 30% with 10% albumin; and in the pentastarch group hematocrit was decreased to 30% with 10% pentastarch. Hematocrit-1 is the average hematocrit over the first 120 min of MCA_O; hematocrit-2 is the average hematocrit over the final 60 min of MCA_O and throughout reperfusion.

* $P < 0.05$ *versus* the control group.

TABLE 2. Evans Blue in the Hemisphere Ipsilateral to Middle Cerebral Artery Occlusion

	Control	Albumin	Pentastarch
Spectrophotometry			
Evans Blue	20.8 ± 9.0	15.5 ± 7.3	4.7 ± 2.7*
Image Analysis			
3.0 mm section	13.2 ± 3.8	8.7 ± 2.7†	4.0 ± 1.7*
5.0 mm section	10.4 ± 3.6	7.3 ± 2.1†	4.0 ± 1.8*
7.0 mm section	6.7 ± 2.1	7.8 ± 2.1	3.0 ± 1.5*
11.0 mm section	0.9 ± 0.7	1.1 ± 0.7	0.9 ± 0.6

The spectrophotometric data are expressed in micrograms per gram brain tissue (mean ± SD), and the image analysis data are expressed as a percent area of Evans Blue extravasation in coronal sections 3.0, 5.0, 7.0, and 11.0 mm posterior to the frontal pole. See table 1 for group definitions.

* $P < 0.05$ *versus* the control and albumin groups.

† $P < 0.05$ *versus* the control group.

± 7.3) groups *versus* the pentastarch (4.7 ± 2.7) group ($P < 0.05$). In two sections, the area of Evans Blue extravasation was greater in the control *versus* the albumin group. In three sections, the area of Evans Blue extravasation was greater in the control and albumin groups *versus* the pentastarch group (table 2). Evans Blue was not visible in the hemisphere contralateral to MCAo.

PART B

In the 3.0-mm section, brain injury was less in the pentastarch *versus* the albumin group ($P < 0.05$; table 3 and fig. 2). For the 5.0-mm section, there was no difference in the area of brain injury. For all cortical areas that were biopsied, specific gravity was greater in the pentastarch *versus* the albumin group. In basal ganglia tissue, there was no difference between the two groups (table 4).

PART C

The histologic findings demonstrated early changes of infarction for both groups (figs. 3 and 4). In the hemisphere ipsilateral to MCAo, edema was qualitatively greater in the albumin *versus* the pentastarch group. Pinocytotic pits, vesicles, and channels were present in the endothelial cells of both groups. In addition, the endothelial cytoplasm was thinner than normal in some areas. In all specimens for both groups, the interendothelial tight junctions were intact in both ischemic and nonischemic hemispheres.

TABLE 3. Area That Did Not Stain with 2,3,5-Triphenyltetrazolium Chloride

	Albumin	Pentastarch
3.0 mm section	45 ± 6	33 ± 8*
5.0 mm section	41 ± 12	38 ± 6

Area (percent of the cross-sectional area for the hemisphere ipsilateral to MCA_O, mean ± SD) that did not stain with 2,3,5-triphenyltetrazolium chloride (brain injury; see fig. 2) in coronal brain slices 3.0 and 5.0 mm posterior to the frontal pole (see fig. 1). See table 1 for group definitions

* $P < 0.05$ *versus* control.

TABLE 4. Micrograviметric Data for Each Hemisphere

	Albumin	Pentastarch
Section 1		
Cortex		
Left	1.035 ± 0.003	1.040 ± 0.003*
Right	1.045 ± 0.001†	1.045 ± 0.002†
Basal Ganglia		
Left	1.043 ± 0.003	1.044 ± 0.003
Right	1.045 ± 0.002	1.046 ± 0.002
Section 2		
Cortex (superior)		
Left	1.034 ± 0.002	1.040 ± 0.002*
Right	1.044 ± 0.003†	1.043 ± 0.003
Cortex (inferior)		
Left	1.031 ± 0.003	1.037 ± 0.003*
Right	1.042 ± 0.001†	1.042 ± 0.002†
Basal Ganglia		
Left	1.042 ± 0.002	1.041 ± 0.003
Right	1.042 ± 0.001	1.043 ± 0.003

Data are mean ± SD.

Section 1 was brain tissue 1.0–3.0 mm from the frontal pole, and section 2 was 5.0–7.0 mm from the frontal pole. See figure 1 for biopsy areas and table 1 for group definitions.

* $P < 0.05$ *versus* the albumin group.

† $P < 0.05$ between the left and right hemispheres.

Discussion

These results support the hypothesis that, in the setting of temporary focal cerebral ischemia, pentastarch reduces BBB permeability and edema. Brain tissue from the pentastarch group was less permeable to Evans Blue and had less water as assessed by microgravimetry and electron microscopy. Pentastarch also effected a decrease in brain injury, which was likely a result of decreased vasogenic edema and its effect on secondary brain injury.[1]

Evans Blue is an indicator dye that is totally bound to serum albumin (for all groups studied) and does not normally cross the BBB in appreciable quantity.[13,15] As observed in pilot studies in this laboratory and in studies by other investigators,[21,22] complete extraction of Evans Blue is effected by incubation of Evans Blue–containing tissue in formamide. We assessed Evans Blue by two methods that address unique aspects of vasogenic edema. The area of Evans Blue staining was determined by image analysis, which estimates the spread of vasogenic edema and the potential for extension of the primary injury.[1,13,15] This data is limited because only area, and not optical intensity, of the color blue was provided. Accordingly, spectrophotometry was used as a direct quantitative assessment of

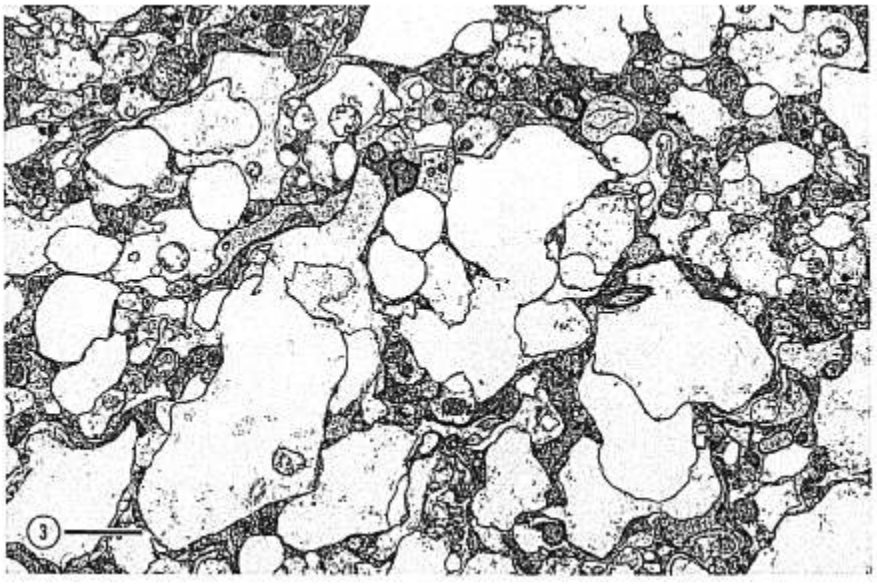

FIG. 3. Electron micrograph: albumin group. The cerebral cortex in this and figure 4 are from the hemisphere ipsilateral to middle cerebral artery occlusion. The astrocytic cytoplasm is edematous, and hypoxic changes are evident. Bar = 2.0 μm (×8,100).

BBB permeability to the Evans Blue:albumin complex (*i.e.*, vasogenic edema).[13,15] Thus, these two methods should be viewed as different pieces of information and not necessarily as validations of each other (*i.e.*, two equal areas of Evans Blue staining could have two different concentrations of Evans Blue, which would effect a darker blue stain in one group). Previous studies[13,15] and the Evans Blue films in this study have validated that the area of Evans Blue staining corresponds to the core area of infarct as measured by TTC stain.

The area of brain injury was measured with TTC, which functions as a proton acceptor for mitochondrial oxidative enzyme systems. Mitochondrial enzymes in normal brain effect a red staining of brain parenchyma. During sustained ischemia, oxidative enzymes are dysfunctional, and a pale area of brain results. There are limitations in the interpretation of TTC data, because the lack of TTC conversion to its red derivative indicates mitochondrial metabolic dysfunction, not absolute and inevitable infarction.[17] However, the goal of this study was to analyze brain injury histologically in the immediate period of reperfusion, and TTC stain was chosen to avoid extending reperfusion beyond 120 min (a necessary delay with conventional light microscopy); such a delay would have provoked additional brain injury and obscured the immediate effects of therapy.

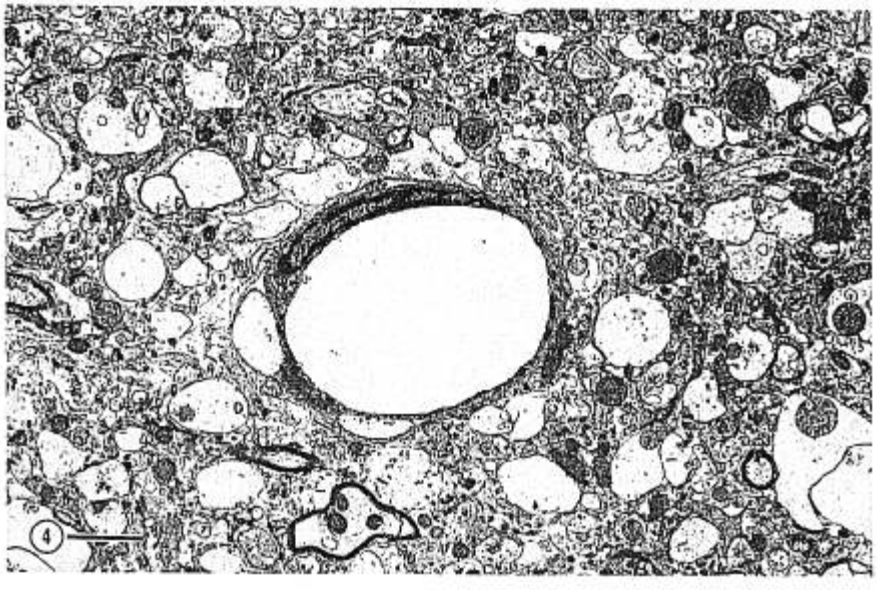

FIG. 4. Electron micrograph: pentastarch group. Compared to figure 3, there is less edema and the microvessel is patent. Bar = 2.0 μm (×8,100).

Hydroxyethyl starch fluids are derived from pectin, which are substituted with hydroxyethyl groups to prolong the intravascular half life. Pentastarch is a low-molecular-weight (average 269 kD), less-substituted (molar substitution ratio 0.45), polydispersed hydroxyethyl starch colloid solution with a restricted molecular weight range (≈ 10–1,000 kD), as compared to hetastarch (Hespan®; molecular weight average 450 kD, substitution ratio = 0.7, molecular weight range ≈ 10–3,400 kD).[23] Pentastarch has been reported to modify the basement membrane and/or have an anatomic sealant action at separated endothelial junctions in ischemic tissue beds.[5–8] The molecular weight range that is reported to be beneficial to an injured microvasculature (100–300 kD) is within the molecular weight range of pentastarch.[6] However, this effect has not previously been tested in the brain.

Results from the present study are consistent with those from recent studies in a variety of models that have shown that hydroxyethyl starch molecules in the 100–300-kD range reduce microvascular permeability.[5–8] In a porcine model of fecal peritonitis, Webb *et al.*[8] demonstrated that 6% Pentafraction® improved capillary patency and alveolar capillary barrier thickness when compared with a 6% higher-molecular-weight hetastarch solution. In burn and ischemia/reperfusion models of endothelial injury, Zikria *et al.*[5–7] established that 6% Pentafraction® reduced the transvascular leak of albumin. It was proposed that this fraction of hydroxyethyl starch physically plugged the separated endothelial junctions of leaky capillaries. This postulate is not supported by the present study, in which electron microscopy did not reveal separation of the tight junctions at a time when there was a substantial transvascular leak of Evans Blue (immediate period of reperfusion). Although we were unable to demonstrate open tight junctions by electron microscopy, the possibility of an earlier opening with closure prior to tissue fixation cannot be dismissed. (The postulate by Zikria *et al.*[5–7] should not be readily dismissed, because there are meaningful differences [*i.e.*, tight junctions, pinocytotic activity] between the blood–organ barrier of brain *versus* the rest of the body.)

Capillary endothelial cells selectively control molecular movement across the BBB. The tight junctions of endothelial cells form a barrier against polar solutes and proteins. Moreover, there is a paucity of pinocytotic vesicles and fenestrae for transcellular vesicular transport.[24] However, cerebral ischemia effects pathologic changes that result in a characteristic time course of edema formation. Early (minutes) in the course of ischemia, cytotoxic injury occurs and results in disruption of transmembrane ionic gradients and cellular swelling (cytotoxic edema). Vasogenic edema develops later (hours), is due to BBB disruption, and involves the transvascular leak of serum proteins into brain parenchyma. However, in the event of reperfusion, there is an immediate and more profound opening of the BBB with substantial vasogenic edema.[13] This opening is associated with postischemic brain injury.[1,3] The transvascular passage of macromolecules during this phase has been hypothesized to occur through separated tight junctions, by increased transcytosis (*e.g.*, vesicular transport, transendothelial channels), or as the result of endothelial destruction.[25,26] In this model of ischemia, frank destruction of the endothelium is unlikely, because the BBB opening at reperfusion is temporary.[13,27] In addition, electron microscopy did not support endothelial destruction. Transient opening of the interendothelial junctions has been reported during a variety of insults (*e.g.*, acute hypertension, cerebral ischemia)[28,29]; however, this mechanism is not supported by electron microscopy. The presence of multiple pinocytotic vesicles and transendothelial channels in the electron micrographs suggests transcytosis of macromolecules as a mechanism of vasogenic edema in this model.[30] Accordingly, a plausible mechanism by which pentastarch reduced vasogenic edema was by reducing transcytosis of serum proteins.

A critique of this study might question the osmotic and oncotic pressures of the two groups. The osmotic and oncotic pressures of pentastarch and albumin were similar.[31] Thus, the observed changes in brain edema cannot be attributed to oncotic or osmotic pressure differences between the albumin and pentastarch groups.[32,33] A second critique of this study might question whether the effects that were observed resulted from hemodilution or from the drug effects of pentastarch. The purpose of this study was to evaluate the effect of pentastarch on the early formation of vasogenic edema (it was not evaluated as a hemodiluting agent). However, to ensure that clinically relevant levels of pentastarch were present at reperfusion, pentastarch therapy was initiated 60 min before reperfusion. Accordingly, a hemodilution effect was introduced, and an albumin hemodilution group was necessary to determine what degree of potential brain sparing was due to a generalized hemodilution effect.

In summary, we evaluated the effects of pentastarch on microvascular permeability and brain injury after temporary focal cerebral ischemia. BBB permeability, brain injury, and cerebral edema were decreased in pentastarch-treated animals. Although an anatomic site of action at the interendothelial tight junction could not be demonstrated, a functional effect through inhibition of transcytosis is suggested.

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