Neuroprotective effects of citicoline on brain edema and blood–brain barrier breakdown after traumatic brain injury

MUSTAFA K. BAŞKAYA, M.D., ACLAN DOĞAN, M.D., A. MURALIKRISHNA RAO, PH.D., AND ROBERT J. DEMPSEY, M.D.

Department of Neurosurgery, Louisiana State University Medical Center, Shreveport, Louisiana; and University of Wisconsin and Veterans Administration Hospital, Madison, Wisconsin

Object. Cytidine 5’-diphosphocholine (CDPC), or citicoline, is a naturally occurring endogenous compound that has been reported to provide neuroprotective effects after experimental cerebral ischemia. However, in no study has such protection been shown after traumatic brain injury (TBI). In this study the authors examined the effect of CDPC on secondary injury factors, brain edema and blood–brain barrier (BBB) breakdown, after TBI.

Methods. After anesthesia had been induced in Sprague–Dawley rats by using 1.5% halothane, an experimental TBI was created using a controlled cortical impact (CCI) device with a velocity of 3 m/second, resulting in a 2-mm deformation. Four sham-operated control animals used for brain edema and BBB breakdown studies underwent the same surgical procedure, but received no injury. Brain edema was evaluated using the wet–dry method 24 hours postinjury, and BBB breakdown was evaluated by measuring Evans blue dye (EBD) extravasation with fluorescein 6 hours after TBI. The animals received intraperitoneal injections of CDPC (50, 100, or 400 mg/kg two times after TBI [eight–10 animals in each group]) or saline (eight animals) after TBI. Traumatic brain injury induced an increase in the percentage of water content and in EBD extravasation in the injured cortex and the ipsilateral hippocampus. No significant benefit from CDPC treatment was observed at a dose of 50 mg/kg. Cytidine 5’-diphosphocholine at a dose of 100 mg/kg attenuated EBD extravasation in both regions, although it reduced brain edema only in the injured cortex. In both regions, 400 mg/kg of CDPC significantly decreased brain edema and BBB breakdown.

Conclusions. This is the first report in which dose-dependent neuroprotective effects of CDPC have been demonstrated in the injured cortex as well as in the hippocampus, a brain region known to be vulnerable to injury, after experimental TBI. The results of this study suggest that CDPC is an effective neuroprotective agent on secondary injuries that appear following TBI.

Key Words • brain edema • blood–brain barrier • citicoline • traumatic brain injury

Abbreviations used in this paper: ACH = acetylcholine; BBB = blood–brain barrier; CCI = controlled cortical impact; CDPC = cytidine 5’-diphosphocholine; EBD = Evan’s blue dye; FFA = free fatty acid; MABP = mean arterial blood pressure; SD = standard deviation; TBI = traumatic brain injury.

Materials and Methods

In this study, we carefully adhered to the animal welfare guidelines set forth in the Guide for the Care and Use of Laboratory Animals published by the United States Department of Health and Human Services. The animals underwent surgery in random order, and outcome assessments were made by investigators blinded to the experimental groups.
Neuroprotective effects of CDPC on traumatic brain injury

Male Sprague–Dawley rats each weighing 250 to 300 g were given 4% halothane to induce anesthesia and 1.5% halothane in a mixture of 50% nitrous oxide/50% oxygen to maintain it. Traumatic brain injury was induced using a CCI device similar to one developed and described earlier.2,6 After each animal was placed in a stereotactic frame, a craniectomy 6 mm in diameter was performed midway between the bregma and the lambda. The dura was kept intact and care was taken not to cause any injury to vascular structures. Each rat in the experimental groups was injured by a CCI device, which had a 5-mm-diameter tip traveling at a velocity of 3 m/second and creating a 2-mm-deep deformation; rats in the sham-operated group were subjected to the same surgical procedure, including craniectomy, but received no cortical impact. The exposed cortex was covered with Surgicel after TBI and the wound was closed with No. 3.0 silk sutures. All animals were allowed to recover from anesthesia, returned to their cages, and allowed free access to standard laboratory food and water. Core and cranial temperatures were monitored using rectal and temporal muscle probes, respectively, in all animals and maintained at ranges of 37 to 38°C for rectal and 36 to 37°C for temporal muscle temperatures by using a heating pad and lamp during the experiments.

In another group of 25 animals (sham-operated controls, saline-treated rats, and rats treated with 50-, 100-, or 400-mg/kg doses of CDPC [five animals in each group]), the left femoral artery was cannulated using a 22-gauge catheter (vascular access Intra-cath; Becton-Dickinson, Sandy, UT) for continuous monitoring of MABP and arterial blood gas levels after induction and maintenance of anesthesia, as mentioned previously. Blood gas concentrations and hematocrit levels in heparinized blood samples (0.15 ml) were measured using a portable blood gas analyzer (I-STAT; Sensor Devices, Inc., Waukesha, WI).

Wet–Dry Method for Brain Edema Measurements

Brain tissue water content, an indicator of brain edema, was measured 24 hours after injury. After the animal was anesthetized according to the same regimen specified earlier, it was killed, the brain was removed, and the left parietal cortex (injury site), contralateral right cortex, and ipsilateral left and contralateral right hippocampus were dissected (Fig. 1). Dissected tissues were placed on preweighed glass tubes and weighed to yield wet weight. After the tissues had been dried by placing them in a desiccation oven at 70°C for 48 hours, they were reweighed to determine water content. Water content is expressed as a percentage of H2O; this was calculated as (wet weight − dry weight)/wet weight) × 100.

Measurement of Extravasated EBD for BBB Integrity

Permeability to EBD was evaluated 6 hours after injury according to the method described earlier.21,22 Evans blue dye (2% in saline, 3 ml/kg) was administered intravenously and allowed to circulate for 60 minutes. To remove the intravascular dye, the animals were perfused with saline through the left ventricle at 100 cm H2O until colorless perfusion fluid was obtained from the right atrium. After decapitation of the rats, the brains were removed, and tissue samples from each of the four brain regions to be studied were removed (Fig. 1). Each tissue sample was weighed, homogenized in 2 ml of 50% trichloroacetic acid (wt/vol), and centrifuged at 10,000 rpm for 20 minutes. Evan’s blue dye was extracted from the tissue by using 50% trichloroacetic acid to dissociate the dye from protein. After centrifugation, the supernatants containing EBD were diluted fourfold with ethanol. For fluorescence measurement, an aliquot was diluted with solvent (50% trichloroacetic acid/ethanol, 1:3). Tissue levels of EBD were quantitated using a spectrophotofluorometer at an excitation wavelength of 620 nm and an emission wavelength of 680 nm. Sample values were compared with those of EBD standards mixed with the solvent (100–1000 ng/ml). Results were expressed in micrograms of EBD per gram of tissue as the means ± SD.

Experimental and Treatment Protocols

Animals were randomly assigned to be sham-operated controls, injured animals treated with saline, or injured animals treated with a CDPC dose of 50, 100, or 400 mg/kg. Saline in a volume of 0.5 ml or CDPC dissolved in 0.5 ml of saline was injected intraperitoneally two times after injury. The first treatment was given 5 minutes after injury in all animals. An additional treatment was given 4 hours after injury in animals in which EBD extravasation was evaluated and 6 hours after injury in animals in which brain edema measurements were made. These time points were chosen on the basis of previous studies, including ours, that showed formation of brain edema and BBB breakdown peaks 24 and 6 hours after experimental TBI, respectively.2

Statistical Analysis

Data are expressed as the means ± SD. Statistical analysis of data was performed using one-way analysis of variance followed by Tukey’s multiple-comparison posttest. A probability value less than 0.05 was considered statistically significant.

Results

Physiological Variables

Physiological variables for the sham-operated controls and injured animals treated with saline or CDPC are presented in Table 1. The surgical procedure did not affect MABP in any animal, including sham-operated control animals. However, the MABP dropped significantly in all animals after injury. This decrease lasted for 1 minute, after which MABP completely recovered in 10 minutes (Table 2). This is a known effect of CCI brain injury on MABP in rats.2 There were no statistically significant differences in physiological variables among the treatment groups during the procedure.

Brain Edema

Traumatic brain injury induced a significant increase in the percentage of water content in the injured cortex and ipsilateral hippocampus (82.2 ± 0.7% compared with 78.6 ± 0.9% in the ipsilateral and contralateral cortices, respectively, and 82.1 ± 0.4% compared with 79.1 ± 0.7% in the contralateral cortex) at 3 hours after injury (Table 1). In the saline group, the percentage of water content in the injured cortex and ipsilateral hippocampus peaked at 24 hours after injury (82.5 ± 0.7% and 82.9 ± 0.4%, respectively). The percentage of water content in the contralateral cortex peaked at 3 hours after injury (82.5 ± 0.8%). In the CDPC group, the percentage of water content in the injured cortex and ipsilateral hippocampus peaked at 3 hours after injury (82.3 ± 0.7% and 82.8 ± 0.4%, respectively). The percentage of water content in the contralateral cortex peaked at 3 hours after injury (82.5 ± 0.8%). There were no statistically significant differences in the percentage of water content in the injured cortex and ipsilateral hippocampus between the saline group and the CDPC group at any time point.

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0.9% in the ipsilateral and contralateral hippocampi, respectively; p < 0.05) (Fig. 2). Treatment with 50 mg/kg CDPC did not show any protective effect on brain edema (Fig. 2). Compared with the saline-treated group, at a dose of 100 mg/kg CDPC reduced the percentage of water content only in the injured cortex (82.2 ± 0.7% compared with 81 ± 0.5; p < 0.05). Compared with the saline-treated group, a 400-mg/kg dose of CDPC significantly reduced the percentage of water content in both the injured cortex and the ipsilateral hippocampus (cortex 82.2 ± 0.7% compared with 80.9 ± 0.7%; hippocampus 82.1 ± 0.4% compared with 81 ± 0.6%; p < 0.05).

Blood–Brain Barrier Breakdown

Traumatic brain injury induced a significant increase in EBD extravasation in the injured cortex and ipsilateral hippocampus (157.1 ± 28.3 µg/g tissue compared with 107.8 ± 36.2 and 101.3 ± 28.3 µg/g tissue in animals treated with 100 and 400 mg/kg CDPC, respectively; hippocampus from 40.1 ± 16.1 µg/g tissue in animals treated with saline to 14.3 ± 6.1 and 23.9 ± 19 µg/g tissue in animals treated with 100 and 400 mg/kg CDPC, respectively; p < 0.05) (Fig. 3).

Discussion

The results of this study show for the first time that CDPC reduces brain edema and BBB breakdown in not only the injured cortex, but also the hippocampus in this model of brain injury in rats. In the present study, CCI brain injury induced significant BBB breakdown and brain edema formation in the injured cortex and the ipsilateral hippocampus. Postinjury administration of CDPC provided significant neuroprotection in a dose-dependent manner in these brain regions. Of these regions, the hippocampus is particularly important because of its selective vulnerability to ischemic changes, even after mild-to-moderate brain injury.

Secondary Injury Factors After Brain Injury

Secondary injury factors, including posttraumatic brain

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**TABLE 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>PO2 (mm Hg)</th>
<th>PCO2 (mm Hg)</th>
<th>pH</th>
<th>Hct (%)</th>
<th>RT (°)</th>
<th>CTemp (°)</th>
</tr>
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<tbody>
<tr>
<td>sham operated</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>preop</td>
<td>138.8 ± 5.9</td>
<td>38.0 ± 2.9</td>
<td>7.31 ± 0.06</td>
<td>32.3 ± 2.5</td>
<td>37.6 ± 0.4</td>
<td>36.8 ± 0.4</td>
</tr>
<tr>
<td>postop</td>
<td>132.5 ± 27.9</td>
<td>39.3 ± 4.5</td>
<td>7.33 ± 0.05</td>
<td>33.7 ± 2.1</td>
<td>37.9 ± 0.2</td>
<td>36.6 ± 0.2</td>
</tr>
<tr>
<td>saline treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preop</td>
<td>159.2 ± 29.2</td>
<td>40.8 ± 2.1</td>
<td>7.38 ± 0.03</td>
<td>35.1 ± 2.1</td>
<td>37.9 ± 0.1</td>
<td>36.2 ± 0.4</td>
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<tr>
<td>postop</td>
<td>159.8 ± 27.3</td>
<td>45.0 ± 0.07</td>
<td>7.34 ± 0.02</td>
<td>34.9 ± 1.1</td>
<td>37.9 ± 0.1</td>
<td>36.3 ± 0.3</td>
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<tr>
<td>CDPC treated</td>
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</tr>
<tr>
<td>50 mg/kg preop</td>
<td>144.0 ± 38.4</td>
<td>37.7 ± 5.9</td>
<td>7.35 ± 0.02</td>
<td>35.4 ± 5.1</td>
<td>37.8 ± 0.2</td>
<td>36.2 ± 0.2</td>
</tr>
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<td>100 mg/kg preop</td>
<td>154.2 ± 33.3</td>
<td>43.4 ± 3.9</td>
<td>7.35 ± 0.04</td>
<td>35.4 ± 4.3</td>
<td>37.6 ± 0.3</td>
<td>36.2 ± 0.2</td>
</tr>
<tr>
<td>400 mg/kg preop</td>
<td>145.4 ± 30.7</td>
<td>40.5 ± 4.5</td>
<td>7.36 ± 0.03</td>
<td>33.8 ± 2.4</td>
<td>37.5 ± 0.08</td>
<td>36.3 ± 0.3</td>
</tr>
<tr>
<td>postop</td>
<td>147.0 ± 31</td>
<td>39.0 ± 8.8</td>
<td>7.33 ± 0.05</td>
<td>34.8 ± 4.4</td>
<td>37.7 ± 0.3</td>
<td>36.3 ± 0.3</td>
</tr>
</tbody>
</table>

* Data are expressed as the means ± SD. Abbreviations: CTemp = cranial temperature; Hct = hematocrit; RT = rectal temperature.

**TABLE 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>Preop MABP (mm Hg)</th>
<th>1 Min</th>
<th>10 Mins</th>
<th>30 Mins</th>
<th>60 Mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>sham operated</td>
<td>92.5 ± 8.7</td>
<td>92 ± 8</td>
<td>92.5 ± 9.6</td>
<td>90.8 ± 8.3</td>
<td>90 ± 8.7</td>
</tr>
<tr>
<td>saline treated</td>
<td>91.2 ± 5.3</td>
<td>77.8 ± 6.3</td>
<td>88.2 ± 7.8</td>
<td>85.7 ± 4.4</td>
<td>88.5 ± 3.9</td>
</tr>
<tr>
<td>CDPC treated</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>50 mg/kg</td>
<td>103.6 ± 5.7</td>
<td>87.8 ± 6.9</td>
<td>94.6 ± 9.6</td>
<td>100.4 ± 8.7</td>
<td>99.4 ± 11.4</td>
</tr>
<tr>
<td>100 mg/kg</td>
<td>93.2 ± 3.5</td>
<td>76.4 ± 7.7</td>
<td>91.8 ± 8.4</td>
<td>89 ± 3.8</td>
<td>88.8 ± 4.5</td>
</tr>
<tr>
<td>400 mg/kg</td>
<td>92.9 ± 5.3</td>
<td>84 ± 10.3</td>
<td>94 ± 14.1</td>
<td>88.7 ± 6.5</td>
<td>89.4 ± 8</td>
</tr>
</tbody>
</table>

* Data are expressed as the means ± SD.
edema and ischemia, are of great importance in patient outcome after head injury. Under a variety of pathological conditions such as TBI, a disruption of the BBB causes vasogenic brain edema. The essential events in the development of vasogenic edema are increased cerebrovascular permeability, enhanced driving forces that induce a bulk flow into the interstitial space, and retention of fluid.1,11 The mechanism by which brain edema is formed after TBI is not yet well defined. Edema formation might be directly related to the injury itself or to the secondary metabolic injury triggered by resultant local cerebral ischemia. Secondary metabolic injury is caused by the upregulation, release, or induction of a number of potentially damaging endogenous neurochemical factors.12 One of these events is the breakdown of membrane phospholipids, which results in release of FFAs including arachidonic acid. Accumulation of arachidonic acid and its vasoactive metabolites, which includes the prostaglandins and leukotrienes, induces brain edema.4 Furthermore, oxygen free radicals produced during arachidonic acid metabolism are also major contributors to cerebrovascular injury after TBI and cerebral ischemia.

Pharmacological Properties and the Neuroprotective Effects of CDPC

Cytidine 5’-diphosphocholine is a key intermediary in the biosynthesis of phosphatidylcholine, an important phospholipid component of cell membranes. When administered exogenously, CDPC is hydrolyzed in the intestinal and in the circulation to form choline and cytidine.17 Later, these two components disperse widely, cross the BBB, and reach the central nervous system, where they are incorporated into the phospholipid fraction of the membrane and microsomes.17 Cytidine and choline also contribute to metabolic functions such as the formation of nucleic acids, proteins, and ACH.

Restoration of the phosphotransferase reaction by CDPC has been shown to prevent the release of FFAs after ischemic brain injury and to help remove diacylglycerol by changing it into phosphatidylcholine.8 After transient global ischemia in gerbils and rats, CDPC has been shown to reduce the release of FFAs as well as prevent the decrease of phosphatidylcholine.8,18 Cytidine 5’-diphosphocholine also restores disrupted cerebral mitochondrial lipid metabolism induced by hypoxic–ischemic injury and attenuates lactate production.9 In focal ischemia–reperfusion injury, long-term administration of a dose of 500 mg/kg CDPC reduced infarction size and improved neurological outcome in rats.16 In spite of experimental evidence in cerebral ischemia that shows the neuroprotective effects of CDPC, there are limited reports regarding its neuroprotective effects on TBI. In a recent study in which the CCI brain injury model was used, Dixon, et al.,7 showed that delayed posttraumatic administration of CDPC attenuated functional deficits 18 days after injury. They also found, for the first time, that in microdialysis studies 100 mg/kg of CDPC increased ACH in the hippocampus. Rao and associates14 demonstrated that CDPC protects CA1 neurons in the gerbil hippocampus 6 days after reperfusion injury. Furthermore, in clinical studies of CDPC conducted in Europe and Japan, neurological improvement was observed with relatively mild side effects. More recently, a

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Fig. 2. Bar graph demonstrating the effect of CDPC on the percentage of water content, an indicator of brain edema after TBI. Traumatic brain injury induced significant brain edema in the injured cortex and ipsilateral hippocampus 24 hours after injury. A dose of 50 mg/kg CDPC did not reduce brain edema in any brain region (eight rats). At a dose of 100 mg/kg, CDPC reduced brain edema only in the injured cortex (eight rats), whereas 400 mg/kg of CDPC (nine rats) reduced brain edema in both the injured cortex and the ipsilateral hippocampus. CC = contralateral cortex; CDP-50, CDP-100, and CDP-400 = CDPC at doses of 50, 100, and 400 mg/kg, respectively; CH = contralateral hippocampus; IC = injured cortex; IH = ipsilateral hippocampus. Letter “a” indicates p < 0.05 compared with sham-operated animals; letter “b” indicates p < 0.05 compared with saline-treated animals.

Fig. 3. Bar graph depicting the effect of CDPC on EBD extravasation, an indicator of BBB permeability after TBI. Traumatic brain injury induced significant BBB permeability in the injured cortex and ipsilateral hippocampus 6 hours after injury. A dose of 50 mg/kg CDPC (eight rats) did not decrease BBB permeability, whereas both 100 (nine rats) and 400 (eight rats) mg/kg doses of CDPC attenuated BBB permeability in the injured cortex and ipsilateral hippocampus. Abbreviations are defined in legend to Fig. 2. Letter “a” indicates p < 0.05 compared with sham-operated animals; letter “b” indicates p < 0.05 compared with saline-treated animals.
double-blind, placebo-controlled, randomized, dose-ranging study has demonstrated favorable outcome at 90 days postinjury in patients with focal ischemic stroke.12

Many different mechanisms have been shown to induce secondary injury after stroke or TBI. Polypharmaceutical or combinational drug therapy is becoming a viable option for future treatment of brain injury.13 Cytidine 5'-diphosphocholine has been combined with MK-801, a noncompetitive N-methyl-D-aspartate receptor antagonist and a basic fibroblast growth factor to reduce infarction size after focal ischemia.13,15 In both studies, combination therapy was synergistically effective in reducing infarction size and improving neurological deficits.13,15 On the other hand, an alternative option to combination therapy might be a single protective agent such as CDPC, which may act through more than one mechanism.

Conclusions

The present study is the first to demonstrate neuroprotective effects of CDPC on secondary injury factors, brain edema and BBB breakdown, in the injured cortex and hippocampus after CCI brain injury in rats. Because it appears that CDPC may exert neuroprotective effects through different pathways and favorable outcome with CDPC has been shown after ischemic stroke, we believe that it may be an ideal agent for future treatment strategies.

References


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Address reprint requests to: Mustafa K. Başkaya, M.D., Department of Neurosurgery, Louisiana State University Medical Center, 1501 Kings Highway, P.O. Box 33932, Shreveport, Louisiana 71130–3932. email: mbaska@lsumc.edu.