Prevention of Ischemic-Hypoxic Brain Injury and Death in Rabbits With Fructose-1,6-Diphosphate

L.A. Farias, MD, E.E. Smith, MD, and A.K. Markov, MD, FACC

Fructose-1,6-diphosphate has been shown to improve neurologic recovery following resuscitation from cardiac arrest and to restore brain electrical activity during hypoglycemic coma in rabbits. In view of these findings, we determined whether fructose-1,6-diphosphate protects the brain during ischemia-hypoxia. We subjected 16 rabbits to hypotension, hypoxemia, and bilateral common carotid artery occlusion. Five minutes after the onset of isoelectric electroencephalograms, seven randomly selected rabbits received 10% fructose-1,6-diphosphate (350 mg/kg bolus followed by 10 mg/kg/min infusion for 90 minutes) and the remaining nine rabbits (controls) received an equal volume of 1.5% NaCl (3.5 ml/kg bolus followed by 0.1 ml/kg/min infusion for 90 minutes). After isoelectricity lasting 7.86±0.8 minutes (mean±SEM) in the treated group and 6.44 ±0.38 minutes in the control group, the rabbits were reinfused with autologous shed blood and reoxygenated and the carotid artery occluders were removed. Treated rabbits recovered electrical activity more rapidly than the controls (p<0.005), and all seven treated rabbits survived. Only two controls (22%) survived (p<0.001), and they were severely disabled. Histology showed extensive cortical necrosis and focal necrosis in the hippocampi and cerebellum of brains from the two surviving controls. Brains from two treated rabbits exhibited minimal neuronal loss limited to the neocortex, and the brains from the remaining five treated rabbits were normal. This study suggests that fructose-1,6-diphosphate protects the brain from ischemic-hypoxic insults. (Stroke 1990;21:606-613)

As the brain has limited reserves of high-energy adenyl nucleotides, impairment of oxidative metabolism during ischemia-hypoxia leads to rapid depletion of adenosine triphosphate (ATP) stores.\(^1\,^2\) Although the rate of anaerobic glycolysis increases in an attempt to compensate for inadequate energy production via oxidative metabolism,\(^3\,^4\) soon brain activity begins to decline because of inhibition of the rate-limiting and highly pH-dependent enzyme phosphofructokinase by lactic acidosis.\(^5\,^6\) Deterioration of the cerebral energy state results in loss of intracellular K\(^+\), depolarization of the neuronal membrane, and influx of Ca\(^{2+}\).\(^1\,^3\) The increase in intracellular free Ca\(^{2+}\) is suggested to precipitate irreversible neuronal damage during ischemia-hypoxia or following reperfusion of ischemic brain by triggering a cascade of events, which may include uncoupling of oxidative phosphorylation, release of neurotransmitters, activation of intracellular enzymes, accumulation of free fatty acids, and generation of oxygen free radicals.\(^1\,^8\,^9\) Thus, it appears that ATP deficit and subsequent intracellular Ca\(^{2+}\) accumulation are the two primary factors in the chain of events leading to irreversible brain injury. Logically, it would be advantageous to prevent ATP depletion during brain ischemia-hypoxia and improve the recovery of ATP-producing metabolism immediately following reperfusion-reoxygenation. Hypothetically, if such an intervention normalized Na\(^+\), K\(^+\), and Ca\(^{2+}\) transmembrane transport, the deleterious sequence of events leading to cell death might be prevented or attenuated. Fructose-1,6-diphosphate (FDP), a glycolytic high-energy intermediate, has been shown to exert substantial therapeutic effect in a variety of shock states and in tissue ischemia.\(^10\,^17\) In experimental hemorrhagic, endotoxin, and traumatic shock,\(^10\,^13\) FDP significantly increased survival and attenuated organ damage. FDP significantly reduced...
mortality in dogs subjected to 5 hours of bilateral hind limb tourniquet ischemia and prevented ischemic renal injury and increased survival following 30 minutes' occlusion of the superior mesenteric artery in rats. The decreased morbidity and increased survival rate observed with FDP administration in such circumstances have been attributed to the proven ability of FDP to enhance anaerobic carbohydrate utilization and ATP production by intervening both as a high-energy substrate and as a metabolic regulator of glycolysis. Recent experimental and clinical evidence also suggests that FDP attenuates additional tissue injury by inhibiting the generation of oxygen free radicals by activated polymorphonuclear neutrophils (PMNs) during ischemia/hypoperfusion and during postischemic reperfusion.

Our interest in the therapeutic effect of FDP in shock and ischemia was stimulated considerably by our recent findings concerning its hitherto unsuspected beneficial effect on reperfused ischemic organs and its peculiar salutary effect on brain function. FDP prolonged survival during severe hypoxemia and improved short-term neurologic recovery of rabbits successfully resuscitated from cardiac arrest. Furthermore, FDP restored electroencephalographic (EEG) activity during hypoglycemic coma in rabbits and improved recovery of neurophysiologic functions after restitution of normoglycemia with glucose. These data indicate that FDP might afford protection to the brain during ischemia-hypoxia. With these concepts in mind, the present study was designed to investigate whether the intravenous administration of FDP to rabbits subjected to ischemic-hypoxic brain insult attenuates brain injury and increases survival.

Materials and Methods

We used 22 adult New Zealand white rabbits (mean±SEM body weight 3.0±0.35 kg). The studies were conducted according to National Institutes of Health policy guidelines on animal care, and the protocol was approved by the Institutional Animal Care and Use Committee. The rabbits were anesthetized with 3% enflurane in 30% O2+70% N2O, intubated with 3.5 mm i.d. endotracheal tube, immobilized with succinylcholine, and mechanically ventilated with a Harvard respirator (South Natick, Massachusetts). Anesthesia was maintained with 0.5% enfurane in 30% O2+70% N2O. Catheters were placed into both femoral arteries for anaerobic sampling of blood, monitoring of arterial blood pressure, and bleeding of the rabbit. An ear vein was cannulated for the administration of fluids and drugs. Both common carotid arteries were exposed through a ventral midline incision in the neck, carefully dissected free, and encompassed loosely with 3-0 silk suture snare. Stainless steel electrodes were placed subperiosteally in both parietal areas and in the frontal zone for recording of the EEG.

Upon completion of the surgical preparation, the rabbits were allowed 30 minutes to stabilize. The experimental protocol is diagramed in Figure 1. Fifteen minutes before the study, the rabbits were given 0.1 mg/kg morphine subcutaneously and 50 units/kg heparin intravenously, and the enflurane was discontinued; mean arterial blood pressure (MABP) was decreased to 60 mm Hg by bleeding the rabbit into a heparinized container. When a MABP of 60 mm Hg was achieved, the succinylcholine and N2O were discontinued. The rabbits were then administered a hypoxic mixture of 6% O2 and 2% CO2 in 92% N2 concomitant with occlusion of both common carotid arteries with the snares. This was considered time 0. Thereafter, hypotension (MABP of 60 mm Hg) was maintained by manual withdrawal or infusion of small amounts of autologous blood. Six rabbits were rejected from the study because they developed severe hypotension (MABP of <40 mm Hg) before randomization to treatment.

Five minutes after the onset of EEG isoelectricity, seven randomly selected rabbits received a bolus injection of 10% FDP (350 mg/kg) followed by an infusion at 10 mg/kg/min of the same solution for 90 minutes. The remaining nine (control) rabbits received an equivalent volume of 1.5% saline given at the same rate (3.5 ml/kg bolus injection followed by an infusion at 0.1 ml/kg/min for 90 minutes) because administration of glucose during brain ischemia has been reported to have deleterious effects. In previous studies we have employed hypertonic saline as a placebo to compensate for the sodium content of FDP, a sodium salt. Therefore, significant differences in plasma osmolality were not expected between the groups.

After at least 5 minutes of isoelectric EEG the rabbits were reoxygenated, both common carotid artery snares were released, and the shed blood was infused over approximately 5 minutes. The minimum duration of EEG isoelectricity was 5 minutes.
because it has been shown that this produces brain damage in rabbits.20 One FDP-treated and three control rabbits were subjected to this minimal insult. During reoxygenation-reperfusion, the rabbits breathed 30% O₂ and were mechanically ventilated until strong respiratory movements and pharyngeal reflexes were present. They were then extubated, and the arterial lines were removed. The wounds were closed and infiltrated with 0.5% bupivacaine, a long-acting local anesthetic.

All rabbits were provided with O₂ by mask for 30 minutes after extubation, but no other resuscitative (only supportive) measures were employed. All surviving rabbits were kept alive for 72 hours, and their ability to walk, eat, drink, and respond to nonpainful stimuli was evaluated by an individual unaware of the treatment given.

Following the 72-hour observation period, the rabbits were anesthetized, intubated, and mechanically ventilated as before. Following a brief washout with heparinized saline, their brains were fixed by transcardiac infusion of buffered formaldehyde (10%) at a pressure of 130–150 mm Hg. In one FDP-treated rabbit, the transcardiac cannula was dislocated during the infusion; therefore, brain histology was not obtained in this rabbit. The brain sections were prepared and interpreted in the Department of Pathology, and the pathologist was blinded to the nature of the study.

Arterial blood gases and pH (ABL4 Acid Base Laboratory, Radiometer America, Westlake, Ohio) and plasma glucose concentrations were measured before study, when the EEG became isoelectric, and at the end of the ischemic-hypoxic period. These parameters were also measured after 5 and 30 minutes of reperfusion-reoxygenation and immediately before extubation. MABP, heart rate, and EEG (DR8 recorder, Electronics for Medicine, White Plains, New York) were monitored continuously until extubation and recorded at the same times as the blood gas determinations. EEG activity was considered recovered when the electrical signal became continuous. Body temperature was monitored rectally and maintained constant using an external heating lamp.

Hemodynamic and metabolic data are expressed as mean±SEM and were evaluated using the unpaired t test. Survival rates of the two groups were compared using the χ² test corrected for continuity; p<0.05 was considered significant.

**Results**

Values for the measured parameters are summarized in Table 1. When the EEG became isoelectric, the overall PaO₂ was 28±1 mm Hg and MABP 59±2 mm Hg. The pH was significantly lower in the FDP-treated rabbits at the end of the ischemic-hypoxic period and after 5 minutes of reperfusion reoxygenation.

For all 16 rabbits, the EEG became isoelectric after 17.75±0.97 minutes of ischemia-hypoxia. The durations of EEG isoelectricity (7.86±0.8 and 6.44±0.33 minutes, FDP-treated and control rabbits, respectively) and the total ischemic-hypoxic times (25.43±0.97 and 24.33±1.49 minutes, FDP-treated and control rabbits, respectively) did not differ significantly. EEG activity recovered after 2.86±0.62 minutes of reperfusion-reoxygenation in the FDP-

### Table 1. Physiologic Parameters Measured Before Study, During Ischemia-Hypoxia, and During Reperfusion-Reoxygenation in Rabbits Treated With 10% FDP or 1.5% Saline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>MABP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>PaO₂ (mm Hg)</th>
<th>PacO₂ (mm Hg)</th>
<th>pH</th>
<th>Glucose (mg/dl)</th>
<th>Hematocrit (%)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before study</td>
<td>16</td>
<td>91±3</td>
<td>296±4</td>
<td>166±10</td>
<td>35±1</td>
<td>7.41±0.01</td>
<td>160±14</td>
<td>35±1</td>
<td>37.4±0.1</td>
</tr>
<tr>
<td>During ischemia-hypoxia</td>
<td>16</td>
<td>59±2</td>
<td>243±13</td>
<td>28±1</td>
<td>41±2</td>
<td>7.16±0.03</td>
<td>235±19</td>
<td>30±1</td>
<td>37.3±0.1</td>
</tr>
<tr>
<td>Isoelectric EEG</td>
<td>16</td>
<td>59±2</td>
<td>243±13</td>
<td>28±1</td>
<td>41±2</td>
<td>7.16±0.03</td>
<td>235±19</td>
<td>30±1</td>
<td>37.3±0.1</td>
</tr>
<tr>
<td>End of ischemia-hypoxia</td>
<td>FDP</td>
<td>7</td>
<td>52±4</td>
<td>220±16</td>
<td>28±1</td>
<td>44±3</td>
<td>6.99±0.02*</td>
<td>272±26</td>
<td>28±1</td>
</tr>
<tr>
<td>Saline</td>
<td>9</td>
<td>59±4</td>
<td>259±19</td>
<td>28±2</td>
<td>38±3</td>
<td>7.11±0.02</td>
<td>220±17</td>
<td>30±2</td>
<td>37.4±0.2</td>
</tr>
<tr>
<td>During reperfusion</td>
<td>5 minutes</td>
<td>FDP</td>
<td>7</td>
<td>100±5</td>
<td>251±14</td>
<td>182±26</td>
<td>44±3</td>
<td>6.93±0.02†</td>
<td>252±24</td>
</tr>
<tr>
<td>Saline</td>
<td>9</td>
<td>98±5</td>
<td>268±13</td>
<td>142±17</td>
<td>43±4</td>
<td>7.00±0.02</td>
<td>267±29</td>
<td>29±2</td>
<td>37.4±0.1</td>
</tr>
<tr>
<td>30 minutes</td>
<td>FDP</td>
<td>7</td>
<td>92±4</td>
<td>275±9</td>
<td>149±7</td>
<td>33±2</td>
<td>7.15±0.03</td>
<td>262±9</td>
<td>—</td>
</tr>
<tr>
<td>Saline</td>
<td>9</td>
<td>91±3</td>
<td>280±9</td>
<td>129±10</td>
<td>35±3</td>
<td>7.13±0.04</td>
<td>314±38</td>
<td>—</td>
<td>37.4±0.2</td>
</tr>
<tr>
<td>Extubation</td>
<td>FDP</td>
<td>7</td>
<td>85±4</td>
<td>281±11</td>
<td>138±19</td>
<td>41±6</td>
<td>7.28±0.05</td>
<td>229±38</td>
<td>34±2</td>
</tr>
<tr>
<td>Saline</td>
<td>9</td>
<td>82±2</td>
<td>289±12</td>
<td>129±12</td>
<td>36±4</td>
<td>7.24±0.03</td>
<td>278±41</td>
<td>33±2</td>
<td>37.4±0.1</td>
</tr>
</tbody>
</table>

* Data are mean±SEM; n, number of rabbits; MABP, mean arterial blood pressure; HR, heart rate; FDP, fructose-1,6-diphosphate.

*tp<0.005, 0.025, respectively, different from saline by unpaired t test.
treated rabbits and after 23.67±5.04 minutes in the controls (p<0.005) (Figure 2). After 1 hour of reperfusion-reoxygenation, all FDP-treated rabbits showed an EEG pattern similar to that observed before ischemia-hypoxia, whereas EEG activity in all control rabbits was characterized by high-voltage, low-frequency waves (Figure 3). FDP-treated rabbits recovered spontaneous breathing after 38±3.39 minutes and controls after 82.50±15.18 minutes (p<0.025).

All seven FDP-treated rabbits survived 72 hours and had no clinically discernible motor or sensory deficit. Two hours after extubation they were able to move freely and had normal responses to nonpainful stimuli, and by 6 hours they drank water and ate normally. Only two controls (22%) were alive after 72 hours (p<0.001). One remained comatose, and hydration was maintained by intravenous infusion of 5% dextrose in water+0.45% saline. The other surviving control required hand feeding, had clear signs of motor deficit in the right front and hind legs, and showed decreased responses to nonpainful stimuli. The other seven controls died in coma between 3 and 36 hours after extubation; four had seizures before they died.

Microscopic examination of the brains of the FDP-treated rabbits revealed no histologically detectable damage (Figure 4) in four and slight damage (minimal cortical necrosis involving <10% of the cortex) in two. One rabbit with slight damage had an isoelectric EEG for 12 minutes and the other for 7 minutes. In the remaining FDP-treated rabbit the histologic studies are not reported because of inadequate fixation; however, this rabbit survived 72 hours without clinically detectable motor or sensory impairment. Brains of the surviving controls showed patchy and confluent necrosis involving ≥40% of the cortex. In addition, foci of necrosis were found in the hippocampi and cerebellum (Figure 4), sites not damaged in the FDP-treated rabbits.

Discussion

A combination of hypoxia and hypotension or unilateral common carotid artery occlusion can produce brain injury in experimental animals. To potentiate the ischemic-hypoxic brain insult, we used a combination of moderate hypotension, moderate hypoxemia, and bilateral common carotid artery occlusion. The tolerance of the brain to this ischemic-hypoxic insult indicates that it is possible to produce an isoelectric EEG for 5 minutes or longer without evidence of cardiovascular failure. Nonetheless, ≥5 minutes of isoelectric EEG produced severe brain damage and a high mortality rate in saline-treated controls, confirming previous observations in rabbits. That seven controls that remained comatose for up to 36 hours showed no evidence of circulatory collapse strongly suggests that death in these rabbits was probably due to severe brain damage. Another factor that must be considered in favor of this assumption is that four controls had seizures before they died. Since the other three controls died during the night, we can only surmise that they had similar outcomes. The absence of motor deficits and behavioral abnormalities in rabbits treated with FDP appears to be related to the significantly faster recovery of their EEGs and spontaneous breathing following reperfusion-reoxygenation. These results are in general agreement with those obtained by Gurvich for posts ischemic recovery of EEG activity in relation to the amount of brain injury. Since EEG activity returned significantly faster in FDP-treated rabbits than in controls and since the duration of brain ischemia-hypoxia did not differ significantly between the groups, FDP must have protected the brain from injury. Our results indicate that the salutary effect of FDP in ischemic brain is apparently not related to improved cardiovascular and pulmonary function because MABP, heart rate, PaO2, and PaCO2 returned to preischemic values in both groups after ≤5 minutes of reperfusion-reoxygenation. Furthermore, the two surviving controls showed no clinical evidence of circulatory collapse.
Brain ischemia causes failure of both aerobic and anaerobic metabolism, which is reflected in the rapid depletion of ATP stores. ATP is required to maintain both ion gradients across the neuronal membrane and synaptic transmission and thus EEG activity. During ischemia-hypoxia these functions cease, probably as a result of inadequate ATP generation. In addition, it has been shown that the recovery of these electrophysiologic functions following reperfusion is closely associated with improvement of energy-producing metabolism. Therefore, to explain the rapid recovery of EEG activity and its return to the
preischemic pattern after ≤60 minutes of reperfusion-reoxygenation, FDP might have increased ATP production via glycolysis immediately upon reperfusion-reoxygenation. Such an increase in ATP generation may have accelerated the recovery of neuronal membrane functions (e.g., ion pump activity) and provided energy for synaptic transmission. This possibility is consistent with our previous report that FDP administration induced a return of EEG activity during hypoglycemic coma and that EEG activity recovered a pattern similar to that before the coma following resolution of the hypoglycemia with glucose. It has also been shown that systemic administration of FDP prolongs the time required for the EEG to become isoelectric during anoxemia and improves the reoxidation of cytochrome a during reoxygenation of cat brain.

Histologic evaluation demonstrated that the brains of controls that survived >48 hours exhibited extensive necrosis of the neocortex as well as focal necrosis in the hippocampi and cerebellum, whereas FDP-treated rabbits subjected to the same or more severe ischemic-insult had less histologically detectable injury, consisting of small confluent foci of necrosis limited to the neocortex. This beneficial effect of FDP is exemplified by the histologic findings in one rabbit in which the EEG was isoelectric for 12 minutes; <10% necrosis in the neocortex was demonstrated. Thus, it is evident that ischemia-hypoxia leading to EEG isoelectricity lasting 5 minutes or longer produces neuronal damage and that FDP administration in such circumstances attenuates the brain injury.

The precise mechanism by which FDP increases survival and attenuates brain damage following brain ischemia-hypoxia is difficult to explain. However, the ability of FDP to sustain glycolysis and increase ATP production in an oxygen-deficient environment may be responsible for the improved neurologic outcome of our rabbits. Systemic administration of FDP during ischemia and hypoperfusion increases ATP levels in the myocardium, liver, kidney, intestine, and skeletal muscle. It is thus reasonable to assume that FDP improved anaerobic carbohydrate utilization in the brain, thereby attenuating brain injury and increasing survival. Enhanced glycolysis during ischemia-hypoxia and immediately following reperfusion-reoxygenation could supply energy to meet neurons’ needs for the maintenance of ion gradients and cell membrane integrity. Studies in vascular smooth muscle and isolated heart indicate that glycolytically produced ATP in the cytosol is more important for the maintenance of cell membrane functions than is ATP produced by mitochondria. Furthermore, since cell membrane failure apparently precedes the development of ischemic infarction, prevention of membrane disruption during ischemia-hypoxia and early recovery of membrane function following reperfusion-reoxygenation might explain the lesser degree of cortical infarction in FDP-treated rabbits. The possible protective effect of FDP on the cell membrane is further supported by observations that FDP prevents K+ loss during acute myocardial ischemia and from stored erythrocytes, reduces mortality from lethal doses of KCl, and attenuates hemolysis during extracorporeal circulation. Besides improving the rheologic properties of erythrocytes, FDP increases their 2,3-diphosphoglycerate (DPG) levels. These findings indicate that FDP may have membrane-stabilizing properties.

Although the issue of whether FDP enters cells remains controversial, recent studies appear to demonstrate that FDP crosses biologic membranes (including the blood-brain barrier) and is actively metabolized. Recently, Gregory et al reported that FDP protects astrocytes subjected to 18 hours of normothermic anoxia. In addition, these authors measured the uptake of radiolabeled FDP and found it to be rapidly incorporated into the cell fraction of normoxic astrocytes. Since we found blood glucose concentrations to not differ between groups, it is likely that FDP was used as an alternate substrate by the brain.

Another possible explanation for the beneficial effect of FDP in this model of brain ischemia-hypoxia is that FDP prevented the generation of oxygen free radicals during ischemia-hypoxia and reperfusion-reoxygenation; oxygen free radicals are considered an important factor contributing to the development of brain edema and irreversible ischemic brain injury. During ischemia, neurons accumulate Ca2+ and free fatty acids, which in turn initiate the generation of oxygen free radicals. Since FDP has been shown to inhibit Ca2+ uptake in stored spermatozoa, it is likely that FDP prevents Ca2+ influx by providing energy for the ion pump. FDP may have also decreased the generation of oxygen free radicals via the xanthine oxidase system by attenuating the depletion of high-energy adenyl nucleotides and their subsequent degradation to hypoxanthine. Finally, FDP may prevent the generation of oxygen free radicals by neutrophils during reperfusion-reoxygenation. Infiltration of cerebral ischemic tissues by PMNs is a constant feature, and PMN activation has been reported in patients suffering from acute cerebral ischemia. Also, it has been reported that activated PMNs may play an important role in the development of posts ischemic delayed hyperperfusion and that granulocytopenic dogs subjected to brain ischemia show fewer alterations in cerebral blood flow than do dogs with normal leukocyte counts. FDP has been reported to abolish the respiratory burst and the generation of superoxide by stimulated canine and human PMNs by inactivating the enzyme 6-phosphogluconate dehydrogenase and thereby inhibiting the activity of the hexose monophosphate shunt, which is a major source of oxygen free radicals in PMNs. It has been suggested that PMNs are involved in the pathogenesis of adult respiratory distress syndrome (ARDS) by injuring the pulmonary vascular endothelium with the oxygen free radicals they release. Administration of FDP to
patients with ARDS significantly improves their hemodynamic and pulmonary function parameters. Therefore, by utilizing FDP to prevent the generation of oxygen free radicals by PMNs, one could theoretically attenuate the damage to biologic membranes and other cellular structures, decrease the vascular permeability that results from lipid peroxidation of endothelial cells, and reduce the damage to surrounding tissues. Thus, the brains of our FDP-treated rabbits may have better tolerated the ischemic-hypoxic insult, maintained cellular integrity, and recovered normal function following reperfusion-reoxygenation.

Our purpose was to present experimental data documenting the therapeutic effect of FDP in brain ischemia-hypoxia. Although our study did not address the possible mechanisms by which FDP affords brain protection and prevents death in this experimental model, the possibilities discussed are suggested as subjects for further studies.

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**KEY WORDS**  
anoxia • cerebral ischemia • metabolism • rabbits
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