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Cerebral energy metabolism following ESWL brain injury model and effects of cerebral protective drugs

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The goal of this study was to introduce a new method inducing an experimental brain injury model using ESWL(Extracorporeal Shock Wave Lithotripsy) and to evaluate findings of localized lesions on ^{1}H MR imaging and the response of cerebral energy metabolism using a ^{31}P MR spectroscope to the ESWL brain injury in cats. This study also examined effects of cerebral protecitive drugs.

1) *There were no statiscally significant changes in pH at all measurement points.*
2) *In the trauma group, initial decrease of PCr/Pi was seen at 30 to 60 minutes with return to control levels by 2 hours after injury($P<0.05$), followed by a second decline at 4 hours which lasted until 8 hours after injury.*
3) *Significant recovery in PCr/Pi($P<0.05$) was observed in both the THAM and dexamethasone treated groups at all measurement points and in the mannitol treated group only temporary recovery at 30 and 60 minutes($P<0.05$).*
4) *High intensity signals were seen on ^{1}H MR imaging in traumatized animals.*

This study demonstrated the immediate and persistent recovery of cerebral energy metabolism using THAM or dexamethasone and an immediate but transient effect with mannitol in traumatized animals.

Key Words : *Cerebral energy metabolism · ^{1}H MR imaging · ^{31}P MR spectroscope · ESWL brain injury, cerebral protective drugs.*

INTRODUCTION

It is now well proven that alterations in cerebral energy metabolism after head injury occur in both clinical and experimental studies(Unterberg et al., 1988). Changes in cerebral energy metabolism are suggested by the presence of lactic acidosis in the cerebrospinal fluid clinically, indicating an increase in anaerobic glycolysis(Cold et al., 1975 ; Crockard & Taylor, 1972 ; Sullivan et al., 1976 ; Unterberg et al., 1988 ; Vink et al., 1987). Furthermore, an increase of tissue lactate(Anderson et al., 1988) has been shown in experimental studies.

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The works indicated that when hypoventilation was superimposed on trauma, which requires a marked increase in oxygen demand where oxygen delivery is inadequate, this would result in relative ischemia as described by Siesjo(Siesjo, 1988) as cerebral blood flow insufficient for adequate oxygen maintenance, but sufficient to supply carbohydrate substrate. This would cause a shift from aerobic (mitochondrial) to anaerobic (glycolytic) pathways of energy production to result in an increase in lactate (Aarabi and Long, 1979; Cold et al., 1975; Crockard & Taylor, 1972; DeSalles et al., 1986; Enevoldsen et al., 1976; Giannotta et al., 1987; Hass, 1975; Inao et al., 1988; Jane et al., 1982; Rabow et al., 1986; Rao et al., 1978; Seitz and Ocker, 1977; Unterberg et al., 1988; Wagner et al., 1985; Zupping, 1970). Direct neurochemical measurements have demonstrated changes in tissue pH and high-energy phosphates after traumatic experimental brain injury in both rats(Nilsson et al., 1977; Nilsson and Ponten, 1977) and cats(Yang et al., 1985).

The goal of this investigation was to introduce a new method inducing experimental brain injury in cats using ESWL, and to evaluate findings of the lesion on ^{1}H MR imaging. The study was also to evaluate the response of the cerebral energy metabolism and the possible effects of cerebral protective drugs. Phosphorus-31(^{31}P) magnetic resonance(MR) spectroscopy was utilized for its unique opportunity for non-invasive and continuous monitoring of tissue pH, PCr, inorganic phosphate(Pi) and adenosine triphosphate(ATP) concentrations in the brain(Unterberg et al., 1988; Vink et al., 1987).

Until recently, methods inducing experimental brain injury have been by either stunner(Yang et al., 1985), fluid percussion(Sullivan et al., 1976), penetrating missile(Crockard et al., 1977) or penetrating drill(Crockard et al., 1982). With the rapid development of nuclear magnetic resonance(NMR) technology, the method of NMR spectroscopy has been widely applied to study metabolic changes in head injury(Anderson et al., 1988; Jane et al., 1982; Unterberg et al., 1988; Vink et al., 1987).

However, the degree of experimentally induced lesions varied depending upon the use of the method and individual experience of each technique producing brain injury to make it difficult to correlate changes in cerebral metabolism and degree of experimentally induced brain lesion in a rather accurate manner. In addition, most NMR spectroscopy used for studies has been 2 to 2.34 Tesla which would result in higher chances of giving relatively less accurate values than expected(Anderson et al., 1988; Jane et al., 1982; Unterberg et al., 1988).

MATERIALS AND METHODS

Materials

Twenty five adult mongrel cats, each weighing 2.5 to 3.5kg, were used for this study. These were randomly selected into 5 groups each containing 5 cats.

Methods

The animals were randomly assigned into five groups.

Group Ⅰ : 5 cats with craniectomy only.
Group Ⅱ : 5 cats with craniectomy and ESWL trauma.
Group Ⅲ : 5 cats with craniectomy and ESWL trauma followed by THAM treatment.
Group Ⅳ : 5 cats with craniectomy and ESWL trauma followed by Dexamethasone treatment.
Group Ⅴ : 5 cats with craniectomy and ESWL trauma followed by Mannitol treatment

Surgical preparation

The 25 cats were anesthetized with intramuscular Ketamine 25mg/kg and Atropine 0.08mg/kg and maintained with 1% halothane(30% Oxygen, 70% Nitrous Oxide) through mechanical ventilation with a Harvad ventilator(15cc/kg, 10-12/min).

A catheter was placed in the femoral artery for pressure monitoring and withdrawl of blood samples. An intravenous route was maintained via the antecubital vein, and the animal was positioned in a head frame. Skin and muscle over the right side of the scalp were retracted and the temporo-parietal bone was exposed. A craniectomy(3×5cm) was made along the right temporo-parietal bone to expose the marginal, suprasylvian, and ectosylvian gyrus for ESWL injury and the double tuned ^{31}P MR spectroscopy surface coil(19mm in diameter) was attached.

Core body temperature, measured by rectal

probe, was maintained at 37-38℃ using soft cottons. The systemic arterial blood pressure was maintained at the range of 120-160mmHg.

Experimental protocol

After surgical preparation of the animal, ^{31}P MR spectroscopic measurements of brain pH, phosphocreatine(PCr), inorganic phosphate(Pi) and β-ATP were obtained and samples of arterial blood were withdrawn for measurement of pH, $PaCO_2$, PaO_2, bicarbonate and base excess.

The ventilator was adjusted to deliver a tidal volume of 15cc/kg at a rate of 12 breaths/minute to maintain $PaCO_2$ at 35±5mmHg and PaO_2 above 100mmHg and bicarbonate was given to correct any base deficit. In the control group(n=5), energy metabolism with ^{31}P MR spectroscopy was measured after craniectomy.

In trauma groups, the animals were subjected to ESWL injury after craniectomy, and were randomly assigned to one of the 3 treatment groups(group Ⅲ-Ⅴ).

Group Ⅲ, which was subjected to ESWL injury was given an initial dose of THAM intravenously and then follwed by an injection(1ml/kg) every hour after trauma for 8 hours.

Group Ⅳ animals were treated with intravenous Dexamethasone 6mg/kg after ESWL injury.

Group Ⅴ animals were treated with 2mg/kg of mannitol after trauma.

At 8 hours after trauma, the animals were sacrificed by intravenous injection of KCl. The brains were removed and fixed with formalin for gross and pathologic examination.

ESWL(Extracorporeal Shock Wave Lithotripsy) brain injury

A third generation Donier MPL(Germany) was used in this experiment. White matter of the right marginal or suprasylvian gyrus was targeted by a doppler ultrasonagraphic guidance. 500 pulse wave with 25KV power was transmitted in each craniectomized animal to produce brain damage.

^{31}P Magnetic Resonance Spectroscopic Technique

The MR spectroscopic measurements were made in a Bruker Biospec 4.7/30(Zurich, Switzerland) with a usable inner diameter of 300mm and a Bo field of 4.7 tesla, and ^{31}P resonant frequency was tuned at 81.049 MHz. Acquisition depth was 9mm, which represented that ^{31}P spectrum containd the signals from the brain volume of 9mm radius from the coil surface(Fig. 1). Round double tuned surface coils(^{1}H(inner diameter : 25mm), ^{31}P(inner diameter : 18mm)) were used for both transmission and reception of the radiofrequency signals.

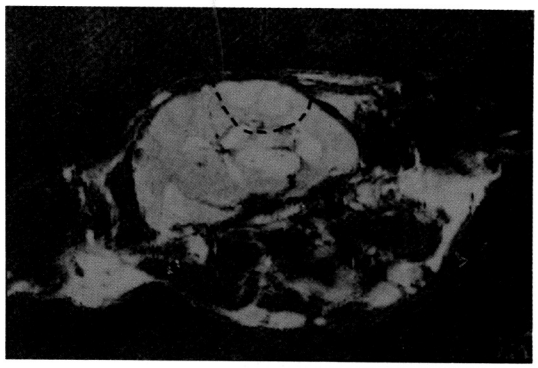


Fig. 1. Area bounded by the dashed line represents the limits of the surface coil sensitive volume(radius=9.5mm) from which the magnetic resonance spectroscopy signals arise.

Magnetic field homogeneity was optimized by shimming on the hydrogen signal from the brain. The spectral width was 6KHz and 16K data points were collected for each scan in an acquisition time of 1.356 seconds. Scans were repeated every 2-3 seconds, and 512 scans were averaged to achieve an adequate signal-to-noise ratio. Total time to obtain an averaged spectrum was 19.6minutes. The area under the Pi, PCr, and the three adenosine phosphate peaks of ATP above an arbitrary baseline was determined in each spectrum by a computerized integration procedure on APS/3000 computer. The intracellular pH was calculated from the chemical shift of the Pi resonance peak relative to the PCr resonance peak using the following equation(Petroff et al., 1985 ; Taylor et al., 1983 ; Zochoden et al., 1988).

$$pH = 6.72 + \log \frac{Pi(shift) - 3.27}{5.69 - Pi(shift)}$$

Confirmation of lesions using ^{1}H MR imaging

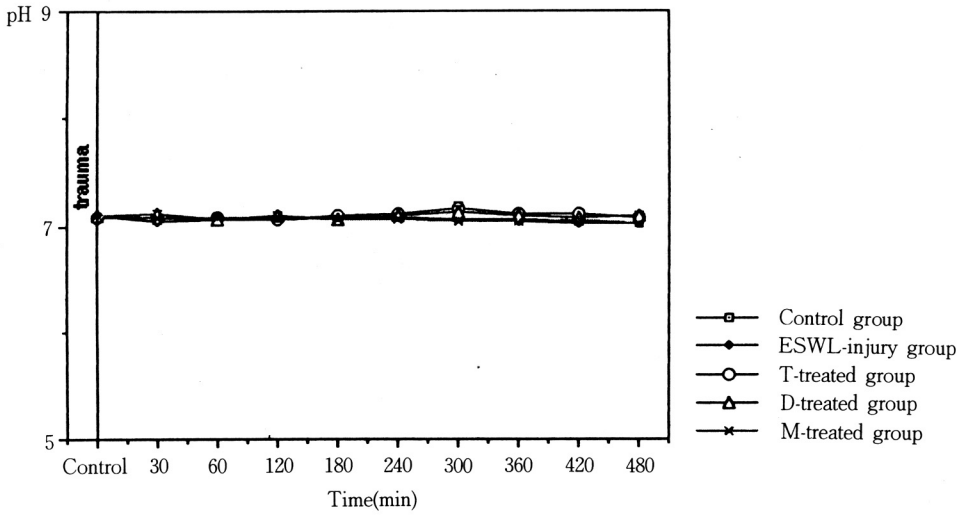
Proton density weighted MR images(TR/TE : 1550/100msec) were followed up in each ex-

perimented animal after 8 hours. Six to seven images were obtained using a multisectional imaging technique. Acquisition matrixes were 256X256 with 8.0cm of field of view(FOV) and 3.0mm slice thickness.

RESULTS

Changes in pH

Values of pH in control animals before and 30 minutes after craniectomy were 7.085±0.015 and 7.077±0.016, respectively. Values of pH in traumatized animals showed 7.090±0.028 before and 7.051±0.022 30 minutes after trauma. There were no statistically significant changes seen in either control or traumatized groups at all measurement points within an 8 hour duration. Values of pH in group Ⅲ(THAM treated after trauma) before and 30 minutes after were 7.082±0.023 and 7.075±0.033, respectively. In group Ⅳ(Dexamethasone treated after trauma) they were 7.103±0.024 and 7.105±0.047 and in group Ⅴ (mannitol treated after trauma) they were 7.089±0.012 and 7.079±0.021,



There were no statistically significant changes in values of pH in all control, traumatized and treated groups at all measurement points from 30minutes until 8 hours.

Table 1. Brain tissue pH level before and at various times after injury*

Study group	control	30min	60min	120min	180min	240min	300min	360min	420min	480min
Control (n=5)	7.085±0.015	7.077±0.016	7.058±0.030	7.059±0.027	7.087±0.038	7.085±0.036	7.065±0.027	7.056±0.024	7.041±0.014	7.028±0.011
ESWL (n=5)	7.090±0.028+	7.051±0.022	7.061±0.023	7.068±0.022	7.097±0.022	7.080±0.016	7.068±0.028	7.052±0.027	7.033±0.027	7.026±0.026
T-treated (n=5)	7.082±0.023+	7.075±0.033	7.073±0.038	7.061±0.013	7.100±0.038	7.108±0.040	7.159±0.067	7.106±0.029	7.112±0.024	7.070±0.015
D-treated (n=5)	7.103±0.024+	7.105±0.047	7.069±0.021	7.096±0.034	7.069±0.029	7.095±0.026	7.127±0.052	7.095±0.026	7.073±0.017	7.094±0.034
M-treated (n=5)	7.089±0.012+	7.079±0.021	7.071±0.016	7.081±0.019	7.056±0.009	7.066±0.012	7.050±0.020	7.042±0.019	7.055±0.021	7.028±0.020

T : THAM D : Dexamethasone M : Mannitol

*Data are means ±standard error of the means.

+ before craniectomy

There were no statistically siginificant changes in valus of pH in all control, traumatized and treated groups at all measurment points form 30minutes until 8 hours.

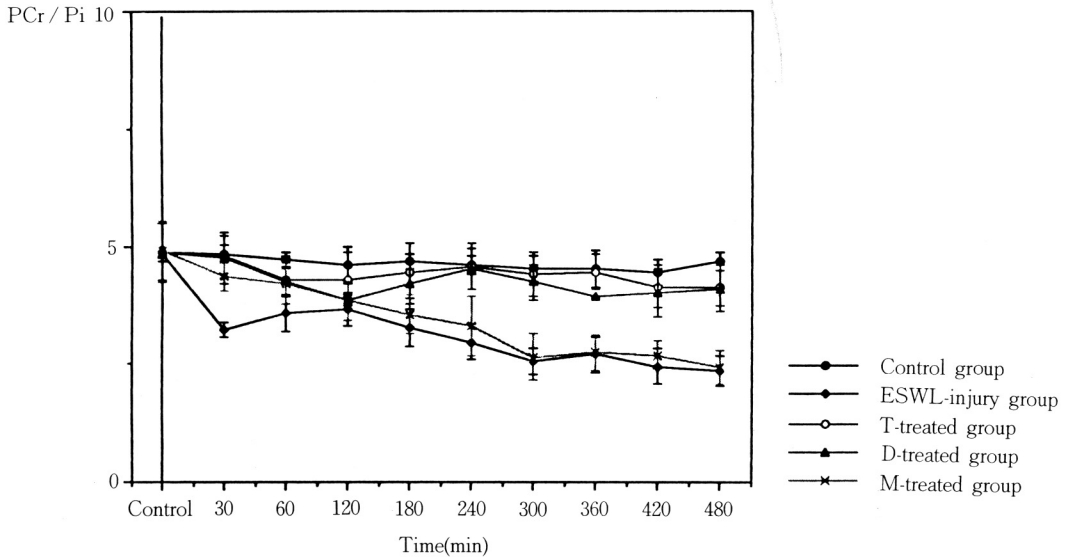


Fig. 3. Graph showing changes of PCr/Pi in the control group(n=5), ESWL trauma group(n=5) and T, D, M-treated group(each group n=5). Changes of PCr/Pi in traumatized animals were found to be biphasic-the initial decrease of PCr/Pi($P<0.05$) was followed by recovery of the changes in 2 and 3 hours to the level of the control group, but significant decrease in PCr/Pi was observed 4 hours after injury (P 0.05). Significant recovery in PCr/Pi($P<0.05$) was observed in both THAM and dexamethasone treated animals at all measurement points from 30minutes after treatment until 8 hours. In the mannitol treated group, recovery of PCr/Pi was noted at 30 minute and 60 minute measurement points($P<0.05$) after treatment, but no significant changes were seen thereafter in comparison with traumatized animals.

Table 2. Phosphocreatine/inorganic phosphate(PCr/Pi) ratio before and at various times after injury*

Study group	control	30min	60min	120min	180min	240min	300min	360min	420min	480min
Control (n=5)	4.879±0.132	4.855±0.187	4.733±0.163	4.589±0.399	4.673±0.165	4.602±0.196	4.534±0.283	4.532±0.401	4.636±0.284	4.670±0.203
ESWL (n=5)	4.854±0.160+	3.212±0.166#	3.562±0.383#	3.647±0.346	3.265±0.391	2.955±0.363#	2.535±0.285#	2.688±0.371#	2.429±0.380#	2.344±0.315#
T-treated (n=5)	4.892±0.607+	4.789±0.448#	4.293±0.514#	4.304±0.576#	4.426±0.656#	4.578±0.495#	4.402±0.487#	4.452±0.376#	4.145±0.467#	4.117±0.369#
D-treated (n=5)	4.874±0.644+	4.754±0.560#	4.253±0.290#	3.859±0.114#	4.214±0.309#	4.520±0.440#	4.231±0.380#	3.917±0.018#	4.015±0.528#	4.102±0.486#
M-treated (n=5)	4.905±0.655+	4.350±0.289#	4.217±0.433#	3.843±0.411	3.547±0.417	3.284±0.642#	2.626±0.500#	2.719±0.387#	2.677±0.307#	2.425±0.367#

T : THAM D : Dexamethasone M : Mannitol

*Data are means ±standard error of the means.

\+ before craniectomy

\# significant difference from control value : $P<0.05$

Changes of PCr/Pi in traumatized animals were found to be biphasic-the initial decrease of PCr/Pi($P<0.05$) was followed by recovery of the changes in 2 and 3 hours to the level of the control group, but significant decrease in PCr/Pi was observed 4 hours after injury($P<0.05$).

Significant recovery in PCr/Pi($P<0.05$) was observed in both THAM and dexamethasone treated animals at all measurement points from 30minutes after treatment until 8 hours. In the mannitol treated group, recovery of PCr/Pi was noted at 30 minute and 60 minute measurement points($P<0.05$) after treatment, but no significant changes were seen thereafter in comparison with traumatized animals.

respectively. Again, there were no statistically significant changes in values of pH in each traumatized and treated animal group at all measurement points from 30 minutes until 8 hours after injury(Fig. 2 and Table 1).

Changes in PCr / Pi

Measurements of PCr/Pi in control and traumatized animals are shown in Fig. 3 and Table 2. Values of PCr/Pi in control animals before and 30 minutes after craniectomy were 4.879±0.132 and 4.855±0.187, respectively and in traumatized animals before and 30 minutes after trauma were 4.854 ±0.160 and 3.212±0.166 respectively. Decrease in value was also seen one hour post-trauma with 3.562±0.383 showing significant changes($P<0.05$). In traumatized animals, PCr/Pi recovered in 2 and 3 hours showed no significant difference compared with the control group, but significant decreases in PCr/Pi($P<0.05$) were again observed 4 hours after injury until 8 hours in comparison with the control group. Significant recovery in PCr/Pi($P<0.05$) was observed in both THAM and dexamethasone treated animals at all measurement points from 30 minutes after until 8 hours. In the mannitol treated group, recovery of PCr/Pi was observed at 30 minute and 60 minute measurement points($P<0.05$) after treatment, but no significant changes were seen thereafter in comparison with traumatized animals(Fig. 3 and Table 2).

Changes in ATP

The time course of the changes in β-ATP in each group is shown in Table 3. Values of β-ATP in control animals before and 8 hours after craniectomy were 43.54±5.86 and 45.45±4.87, respectively and in traumatized group before and 8 hours after were 46.36±4.72 and 47.80±6.04, respectively, showing no significant differences between control and traumatized groups. Observation also con-

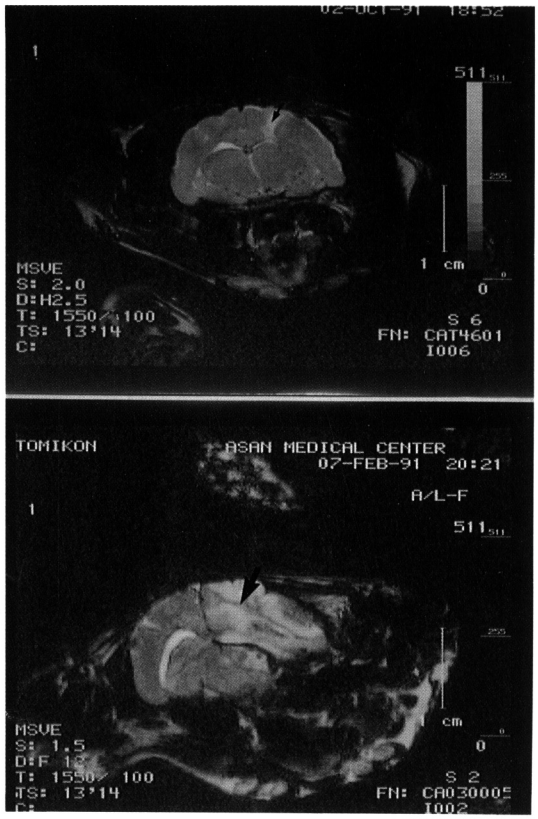


Fig. 4. ESWL(24KV, 500× shock wave)-induced non-hemorrhagic cerebral contusion(A, B). Proton density WI(SE 1550/100) MR scans show irregular shaped high signal lesion in the white matter of the right cerebrum(arrows) 8 hour after injury.

Table 3. Beta-Adenosine Triphosphate(β-ATP) levels before and at various times after injury*

Study group	control	8hr
Control	43.54±5.86	45.45±4.87
ESWL	46.36±4.72	47.80±6.04
T-treated	48.52±6.33	46.49±6.21
D-treated	49.94±6.25	47.51±4.72
M-treated	48.50±5.25	45.39±5.56

T : THAM D : Dexamethasone M : Mannitol

*Data are means ±standard error of the means. The β-ATP values were not significantly changed during the entire experimental period.

cluded no statistically significant difference between traumatized each treated group(Table 3).

Changes in ^{1}H MR Imaging

High signal densities were observed in both the gray and the white matter of the brain without any mass effect or signal changes in the brain stem on proton density of MRI scan in every traumatized animal at the end of an 8 hour measurement point-(Fig. 4).

Changes in Neuropathology

Macroscopic and microscopic neuropathological examinations were performed on all brains. Gross examination showed localized areas of varying degrees of cortical contusion at marginal, suprasylvian and ectosylvian gyri(Fig. 5). Microscopic neuropathological examination of the traumatized brain revealed varying degrees of petechial hemorrhages in the cortex(Fig. 6), but no definite differences were observed on H and E stain in areas between normal and abnormal brain tissues in the vicinity of the high signal on MR Imaging.

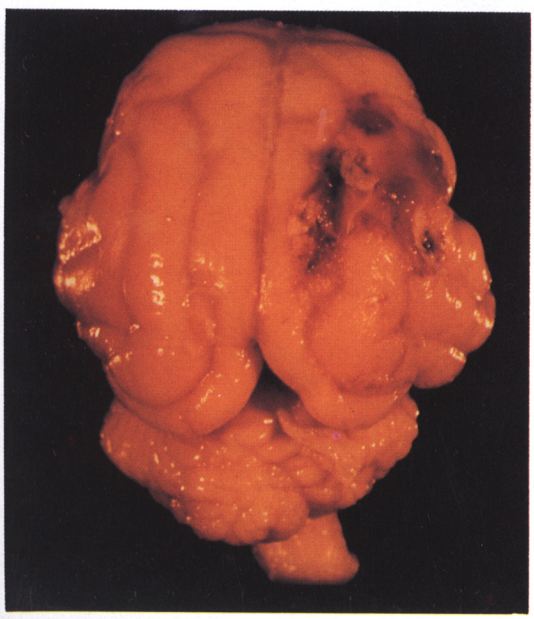


Fig. 5. Dorsal view of feline cerebral hemispheres showing cortical contusion at marginal, suprasylvian and ectosylvian gyri. Normal gyri are shown on the left hemisphere.

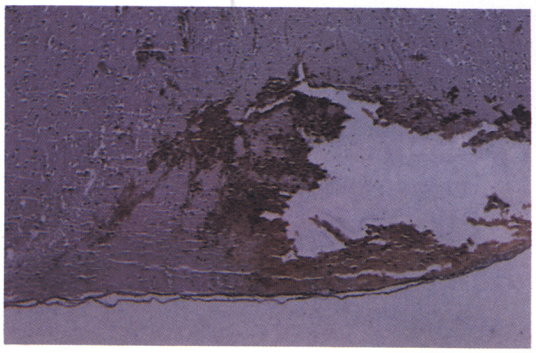


Fig. 6 Cortical intracerebral hemorrhage(ICH) at the lesion site after ESWL injury(H & E stain, ×100).

DISCUSSION

Among the various methods inducing experimental brain injury, there have been substantial studies accumulated of fluid percussion induced brain lesion using NMR technology. However, the produced lesions were not constant, which makes it difficult to correlate with the changes in cerebral metabolism and the degree of experimentally induced brain lesion in an accurated manner(Anderson et al., 1988 ; Ishige et al., 1987 ; Unterberg et al., 1988 ; Vink et al., 1987).

ESWL(Extracorporeal Shock Wave Lithotripsy) originally designed to destroy kidney stones, was used to make the focal brain lesion in this study. During the treatment of kidey stones, subcapsular or perirenal bleeding was the most commonly experienced adverse effect, directly attributable to the externally applied shock waves(Knapp et al.,1988).

The extent of the renal injury by shock waves solely depended on the energy(generator voltage) applied. The rupture of small veins in the kidney, caused by the cavitation bubble in the path of shock waves, induced intraparenchymal hematoma and other secondary effects. Injury to the renal cells was also produced by the high pressure of shock waves(Delius et al., 1988. Eisenberger et al., 1991 ; Lingeman et al., 1989 ; Newman et al., 1987).

The following reasons were presumed in making the experimental brain injury model using ESWL attractive.

1) Since renal injury resulting from ESWL therapy has been frequently documented through various imaging techniques and laboratory stu-

dies, conversely adverse effects of ESWL can be used for creation of focal lesions in the brain.

2) Lesions involving both the gray and white matter of the brain may be made selectively by ESWL focused shock waves. Fluid percussion brain injury which has been most frequently used in inducing experimental brain injury often accompanied subarachnoid hemorrhage or petechial hemorrhages in the thalamus and/or brain stem in addition to the target area(Anderson et al., 1988 ; Ishige et al., 1987 ; Unterberg et al., 1988 ; Vink et al., 1987).
3) The model is simple and reproducible.

In this study, 500 shock waves were delivered to craniectomized cats to induce high signal focal lesions on the proton density-weighted MRI scans. Lesions were varied in size and shape. A few presumptions were brought to account for having various sized lesions induced by ESWL shock waves. Firstly, technical problems of focusing on the target may influence the results. When shock waves were given to the animal, the convex surface of the reflector of the ESWL should be in contact with the convex surface of the craniectomized brain. Thus, the high pressure of shock waves delivered may cause the reflector to vibrate away from the original aim. Secondly, different individual responses to the ESWL injury might have brought such results. In a clinical study, abnormal lesions in MRI were found in 63-85% of the treated human kidneys(Recker et al., 1990).

There has been a wide scope of studies done of metabolic changes in head injury using the technique of NMR spectroscopy. The value of PCr/Pi in group I was 4.9±0.13 which was similar to previously published values found in rats(Petroff et al., 1985 ; Shoubridge et al., 1982 ; Vink et al., 1987), dogs(Shoubridege et al., 1982), and humans(Bettomley et al., 1984). Various results were reported in changes of PCr/Pi after a fluid-percussion injury. Moderate injury(3.2 atm) in cats did not alter its value(Nilsson et al., 1977 ; Recker et al., 1990 ; Unterberg et al., 1988). But suvere injury(4-5 atm) in rats caused a transient decrease in PCr/Pi which returned to normal after 30 min(Ishige et al., 1987 ; Nilsson and Ponten, 1977 ; Vink et al., 1987). In another report, a biphasic decrease was the result of a moderate injury(2.1±0.4 atm) and a high injury(3.9±0.9 atm) in rats and a sustained decrease followed a severe injury(5.9±0.7 atm)(Vink et al., 1987).

Our results were biphasic decline of PCr/Pi as shown in Vink et al(1987). In their study, the degree of decline in PCr/Pi was linearly correlated to the degree of injury. They found the initial decline in PCr/Pi was temporally similar to the changes in H^+ concentration, concluding that a significant fraction of the transient PCr/Pi changes was most likely a reflection of H^+ buffering by the creatine kinase reaction : $PCr+ADP+H^+ \rightarrow ATP+Cr$. Thus, the first decline of PCr/Pi was explained by the reduced capacity of energy production by traumatized brain tissues.

The second deline of PCr/Pi was assumed to be a reduced state of tissue to maintain bioenergetic status due to reduction in mitochondria oxidative phosporlylation(Vink et al., 1987). In 1985, Yang et al, indicated the decrease in PCr without any changes in ATP(Yang et al., 1985). No decrease in ATP levels suggested the reversability of the energy metabolism.

In this study, the initial decrease in PCr/Pi was recovered 2-3 hours after injury, then PCr/Pi declined again.

Several factors to explain the decrease in PCr/Pi following experimental brain injury may be considered. One of the hypotheses is that decrease of the regional blood flow may result in decline in tissue oxygen. But reports have indicated various results, including no changes, temporary decrease of the blood flow followed by increase, or vice versa in animal studies(Duckrow et al., 1981 ; Gaab et al., 1980 ; Gobiet et al., 1976 ; Lewelt et al., 1980 ; Nilsson and Nordstrom, 1977 ; Saunders et al., 1979). An experimental result suggested blood volume to be below 20 ml/100g/min to cause changes in PCr/Pi, which would lead to generalized cerebral edema(Crockard et al., 1982). Thus, the report concluded that decline in tissue oxygen was not the only cause of decrease in PCr/Pi. Another hypothesis is that the decrease of PCr represents abnormalities of energy production to the mitochondrial dysfunction.

The cause of mitochondrial dysfuction was liberation of the free fatty acids, such as arachidonate, which changes the permeability of the inner membrane of mitochondria. The mitochondrial dysfunction and the uncoupling of electron transport are the reasons why ATP production is reduced, which

means the reduction of PCr in the ATP-PCr pool(Ellis et al., 1981 ; Wei et al., 1982).

The reports of the changes in the brain tissue pH are various. The decrease of brain tissue pH was not noted(Yoshida and Marmarou, 1991), or transient decrease which returned to control level within 1 hour without any change of PCr/Pi ratio(Unterberg et al., 1988), or with change of PCr/Pi ratio(Ishige et al., 1987 ; Vink et al., 1987).

In this study, there was no decrease of brain tissue pH level at any time during the injury observation period. There are many reasons to explain such results.

First, the first spectrum was obtained 30-40min after injury because of shimming time which required 15-25min. Therefore, it was possible that the acquired spectrum showed the recovered state of brain tissue pH because immediate change in brain tissue pH could not be observed in our study.

Second, focal brain lesions induced by ESWL at the white matter were identified with proton density weighted MR scans. So, the spectrum acquired using surface coil could include both the traumatized and surrounding normal brain tissue.

Third, the degree of injury induced by ESWL was not so an severe injury as reported in fluid-percussion injury(Vink et al., 1987).

Fourth, physiologic states such as systolic blood pressure, PaO_2, $PaCO_2$, and the animal state were different from the clinical states.

Fifth, mechanical factors which induced focal brain lesion in this study were different from the other brain injury models.

After the experiments, the study evaluated the metabolic changes of brain tissues that occurred with the use of THAM, Dexamethasone and Mannitol on an experimental brain injury and the efficacy of treatment modalities.

THAM, an alkalinizing agent, accepts hydrogen ion(H^+) which allows it to shift the CO_2-HCO_3 equilibrium toward bicarbonate and lower $PaCO_2$, which increases arterial pH and decreases base deficit.

It can cross the plasma membrane and reverse the intracellular acidosis(Nahas, 1963). THAM ameliorated the acidosis of brain tissue and reversed the brain swelling in dogs(Nahas, 1963 ; Rosner and Becker, 1984) and decreased intracranial pressure and rocovered the power spectrum of EEG(Gaab et al., 1980). But, there was no definite recovery of the brain tissue pH levels in a fluid percussion brain injury model in cats(Yoshida and Marmarou, 1991).

In this study, the brain tissue pH levels revealed no change during the 8 hour observation period in both the THAM and the non-treated group. The effects of THAM in regards to the level of the brain tissue pH could not be confirmed because the changes of tissue pH levels were insignificant between the ESWL injury group and the control group. But, the PCr/Pi recovered quickly and was maintained continuously from 30min to 8 hour after injury.

THAM is eliminated in its ionized form with equimolar amounts of bicarbonate, acting at least as an osmotic diuretic. Its effect can relieve the brain edema following brain injury(Goetz et al., 1961 ; Seitz and Ocker, 1977), thus the brain may maintain the energy metabolism in the normal state.

Despite the widespread clinical use of glucocorticoids for the acute treatment of head injury, controversy exists regarding the effectiveness of these druge to enhance survival or neurological recovery-(Braakman et al., 1983 ; Clasen et al., 1965 ; Cooper et al., 1979 ; Dick et al., 1976 ; Faupel et al., 1976 ; Gobiet et al., 1976 ; Gudeman et al., 1979 ; Hall, 1985 ; Maxwell et al., 1975 ; Nelson, 1974 ; Neuenfeldt et al., 1974 ; Pappius and McCann, 1969 ; Pappius and Wolfe, 1983 ; Tornheim and McLaurin, 1978). On one hand, there have been many reports on the use of high dose dexamethasone which have suggested a significant reduction in the mortality rate and improvement in the neurological outcome after head injury(Hall, 1985 ; Maxwell et al., 1975 ; Neuenfeldt et al., 1974 ; Pappius and McCann, 1969 ; Pappius and Wolfe, 1983). In contrast, other reports have failed to document significant objective improvement(Braakman et al., 1983 ; Clasen et al., 1965 ; Cooper et al., 1979 ; Dick et al., 1976 ; Gudeman et al., 1979 ; Nelson, 1974 ; Tornheim and McLaurin, 1978).

In this experiment, high dose dexamethasone was used immediately after injury. The PCr/Pi ratio recovered soon after treatment and was maintained during the 8 hour observation period.

High dose steroids restore energy production in the intracellular mitochondria by the combination of effects such as, inhibition of lipid peroxidation, lipid hydrolysis, inhibition of eicosanoid formation, inhibition of progressive development of post traumatic ischemia, and reversal of intracellular calcium accumulation(Feeny et al., 1981).

The osmotic agent, mannitol can reduce blood

viscosity and relieve brain edema which in turn can reduce intracranial pressure. Lower blood viscosity can increase the cerebral blood flow to the ischemic area after focal infarction(Little, 1978), but only transient effects were reported(Meyer et al., 1987 ; Sundt et al., 1967 ; Sundt and Waltz, 1967).

In this experiment, mannitol was given immediately after trauma. The PCr/Pi was restored 30min. and 60min. after injury, but afterwards there was no effect. The temporary effect of the mannitol may be explained on the basis of relieving early glial edema developing immediately after traumatic neuronal injury, but not for persistent glial edema.

CONCLUSION

In conclusion, the changes in the cerebral energy metabolism that represent reversible focal brain injury by use of ESWL include a biphasic decline of PCr/Pi and no change in the level of brain tissue pH and ATP.

Analyzing the cerebral energy metabolism after injury through the ^{31}P MR spectroscope, this study was able to find improvement of the cerebral energy metabolism immediately and continuously with THAM and Dexamethasone, but only transiently with Mannitol.

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