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# Effects of Dexamethasone in Hypoxic-Ischemic Brain Injury in the Rats

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= Abstract =

## 성숙흰쥐의 허혈-저산소성 병변에서의 덱사메타존의 영향

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The effect of high dose of glucocorticoid in acute spinal cord injury has been well proved experimentally and clinically. In addition. the beneficial effect of steroids in cerebral vasogenic edema has been well documented and clinically steroids are now a part of the treatment of intracranial neoplasms. Consequent trials of high dose steroid therapy in CNS injury have been proved its ineffectiveness or adverse effects in clinical and experimental studies. Also. dexamethasone treatment in hypoxic-ischemic brain damage in rats showed adverse effects on neurons in most of the studies in adult and immature rats, except one report which showed neuroprotective effects of dexamethasone pretreatment in 7-day-old immature rats.

This study was designed to see if there was same neuroprotective effect in adult rat since no previous experiments used same amounts of steroid at this time intervals. Hypoxic-ischemic injury was induced in adult Sprague-Dawley rats, 150~240 gms, by Levine procedure with some modification (left carotid artery ligation and exposure to 8% oxygen-92% nitrogen gas for 2 hours). The animals were divided into four groups and dexamethasone was injected as follows : (I) hypoxic-ischemic control group without dexamethasone injection(n=16) ; (II) 0.5mg/kg i.p. 3 times, 48 and 24 hours, and immediately before the carotid artery ligation and 8% oxygen treatment(n=16) ; (III) 2.0mg/kg at same time with (II) (n=14) ; (IV) 1.0gm/kg 3 times at immediately after, 24 and 48 hours after the procedure(n=20). The neuropathological changes were interpreted 7 days after the procedure.

The results are summarized as follows :

1) In hypoxic-ischemic control group(I), 5 out of 16 rats(31.3%) of rats showed large infarction involving ipsilateral side of the brain and other 4~5 rats showed severe neuronal damage in anterior and posterior cortex, hippocampus, striatum, and thalamus.

2) Compare to control group, dexamethasone 0.5mg/kg 3 times pretreatment group(II) showed similar neuronal damage in all areas, although the infaction was focal in striatum and thalamus

in group II and generalized in group I. The changes were not statistically significant.

3) Group III showed no significant difference from groups I, II, and IV.

4) Group IV showed more neuronal damage in CA1-2 area of hippocampus compare to groups I and II($p<0.01$, $p<0.005$, respectively).

5) Mortality rate was not significantly different between groups.

In conclusion, dexamethasone pretreatment did not improve hypoxic-ischemic neuronal damage in adult rats. Dexamethasone posttreatment aggravated neuronal damages in CA1-2 area of hippocampus compare to control and pretreatment groups.

KEY WORDS : Hypoxic-ischemic brain injury · Dexamethasone.

## Introduction

The pathophysiologic mechanism of irreversible brain damage following cerebral ischemia has been extensively studied without much success. Recently the free radicals or other compounds transformed from free fatty acids(FFAs), especially arachidonic acid which is released during ischemia have been suggested to participate in irreversible brain cell damage[1-4]. They are transformed either nonenzymatically or by cyclooxygenase and lipoxygenase[5-6]. Dexamethasone, the inhibitor of phospholipase $A_2$ activity, and cyclooxygenase inhibitors which blocks the oxidative conversion of arachidonic acid to prostaglandins are beneficial to curtail the production of free radicals[7-8].

Glucocorticoids have been extensively used for treatment of various neurologic disorders and beneficial effects have been demonstrated in human spinal cord injury[9] as well as in experimental spinal cord trauma[10]. It also reduces the cerebral edema due to brain tumors[11-13] and brain trauma[14]. Glucocorticoid therapy in cerebral hypoxia-ischemia did not appear to be effective in reducing brain damage and clinical and experimental studies showed adverse effects of glucocorticoids[15-18], except one study showing neuroprotective effects of low dose dexamethasone pretreatment in 7-day-old immature rats[19].

In this study, the effects of different dosage and administration time of glucocorticoid on the extent of brain damage produced in a model of cerebral hypoxia-ischemia in the adult rats was investigated. The results demonstrated dexamethasone pretreatment did not improve or aggravate the neuronal damages constrast to posttreatment deleterating neuronal damages in CA1-2 area of hippocampus.

## Material and Method

Adult Sprague-Dawley rats weighing 150~240 gms were used for the experiments. The animals were given commercial food pallets and tap water. Dexamethasone (9α-fluoro-16-α-methylprednisolone, Sigma) was dissolved in physiological Ringer's solution before injection.

The animals were divided into 4 groups. Group I was the hypoxic-ischemic control group without dexamethasone injection($n=33$), group II was injected 0.5mg/kg of dexamethasone 3 times intraperitoneally, 48 and 24 hours and immediately before the carotid artery ligation and 8% oxygen treatment ($n=28$), group III was given 2.0gm/kg at same time with group II($n=32$), and group IV was given 1.0 gm/kg 3 times at immediately after, 24 and 48 hours after the procedure($n=48$).

Ischemia and hypoxia were induced with Levine procedure with some modification. Left carotid artery was exposed, isolated from nerve and vein, and ligated with surgical silk under the Ketamin anesthesia. The wound was then sutured and the animal allowed to recover for 3 hours. The duration of

procedure was less than 15 minutes in all cases. Sham-operated animals underwent the same operative procedure except that the exposed carotid artery was not ligated.

After 3 hours of recovery the rats were put into plastic box with four chambers, which was kept in water bath (thermostatically regulated to 37°C) and exposed to 8% oxygen and 92% nitrogen gas for 2 hours. The gas was continuously flowing into plastic box at the speed of 1.5 liter/hour through inlet on one side of the box and coming out through outlet at the opposite side.

Those rats surviving hypoxia were kept in cages for 7 days. They were then anesthetized with ether and their brains were perfusion-fixed via the ascending aorta with 1 : 1 : 8 mixture of formaldehyde, glacial acetic acid, and absolute methanol(FAM).

The brains were removed and stored in FAM for macroscopic and microscopic examination. One week following ischemia-hypoxia was chosen as the time for assessment of damage, because by that time the final neuronal necrosis is fully developed. Controls consisted of animals subjected to unilateral ligation of common carotid artery without subsequent hypoxia(n=5), hypoxia without prior ligation(n=5), and neither ligation nor hypoxia(n=5).

The FAM-fixed forebrain was cut coronally through the pituitary stalk and blocks of 3 mm thickness. Right hemisphere was inked and each blocks were embedded in paraffin. Sections of 8μ thick were stained with hematoxylin and eosin. Extent of ischemic neuronal alterations were evaluated as the crude damage index observed in anterior and posterior cortex, hippocampus, striatum, and thalamus as follows ; 0 : no damage(Fig. 1), 1 : neuronal damage in less than 10% of cells, 2 : neuronal damage in less than 50% of cells, 3 : neuronal damage in more than 50% of cells (Fig. 2), and 3 * : infarction(Fig. 3).

Results were analyzed using analysis of variance. A post hoc comparison was performed between the experimental animal groups using Student's test and

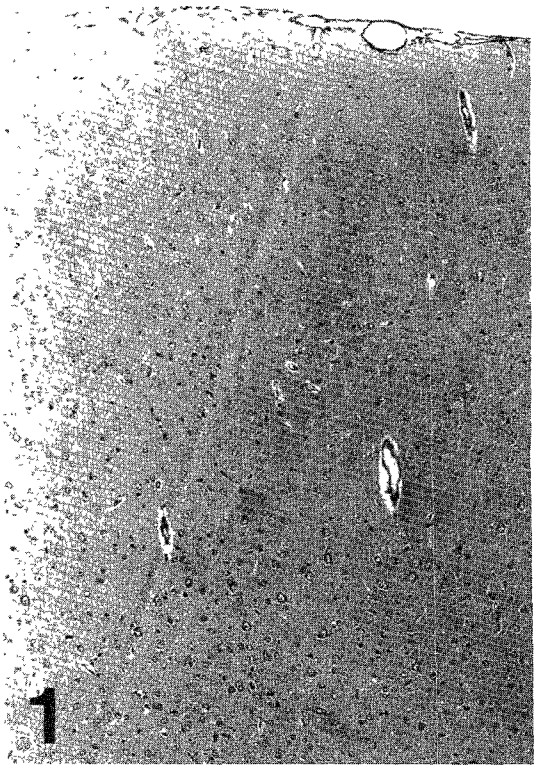

Fig. 1. Normal cerebral cortex (H-E, ×25 original magnification).

ANOVA test for multiple comparisons ; p values of $<0.05$ were considered as significant differences.

## Results

Mortality rate was 51.5% in hypoxic-ischemic control group(I), 42.9% in 0.5mg/kg pretreatment group(II), 56.25% in 2.0mg/kg pretreatment group (III), and 58.3% in 1.0mg/kg post-treatment group (IV) (Table 1).

Mild to moderate brain swelling of left cerebral hemisphere was noted in the brains of 17 rats with infarction. In coronal sections of the cerebrum, shift of midline structures was not observed. Softening and gray discoloration were noted in ipsilateral cortex and hippocampus of those rats with infarction.

There were no alterations in the brains of 15 control rats. In hypoxic-ischemic control group(I), 5 out of 16 rats(31.3%) showed large infarction in-

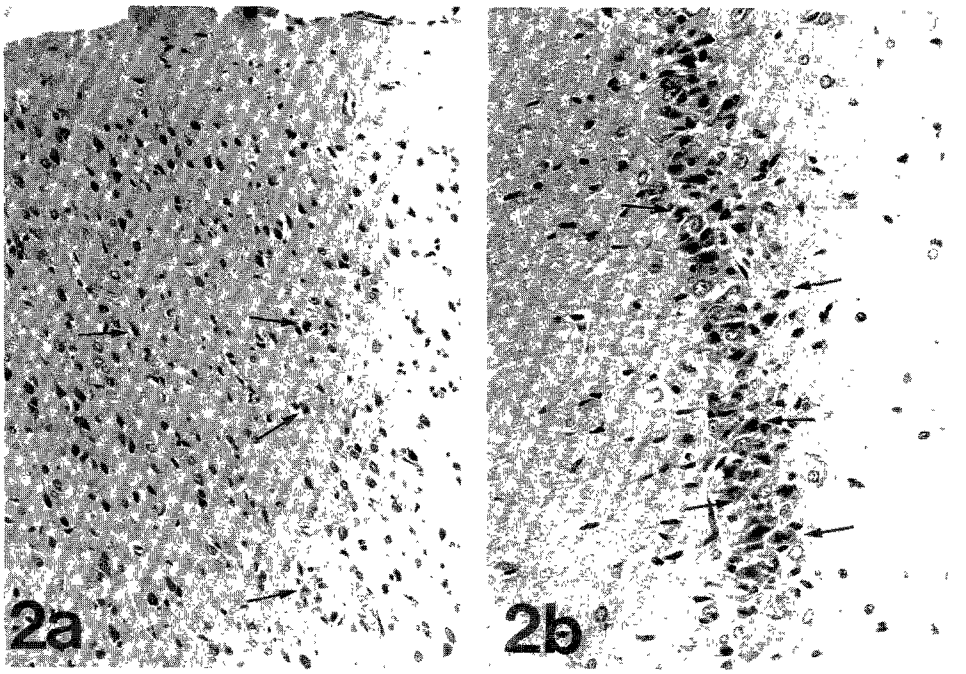


Fig. 2. Degeneration of more than 50% of neurons : Eosinophilic degeneration of neurons are noted (arrows)
A : Cerebral cortex (H-E, ×50 original magnification)
B : Cornus ammonis of hippocampus (H-E, ×80 original magnification)

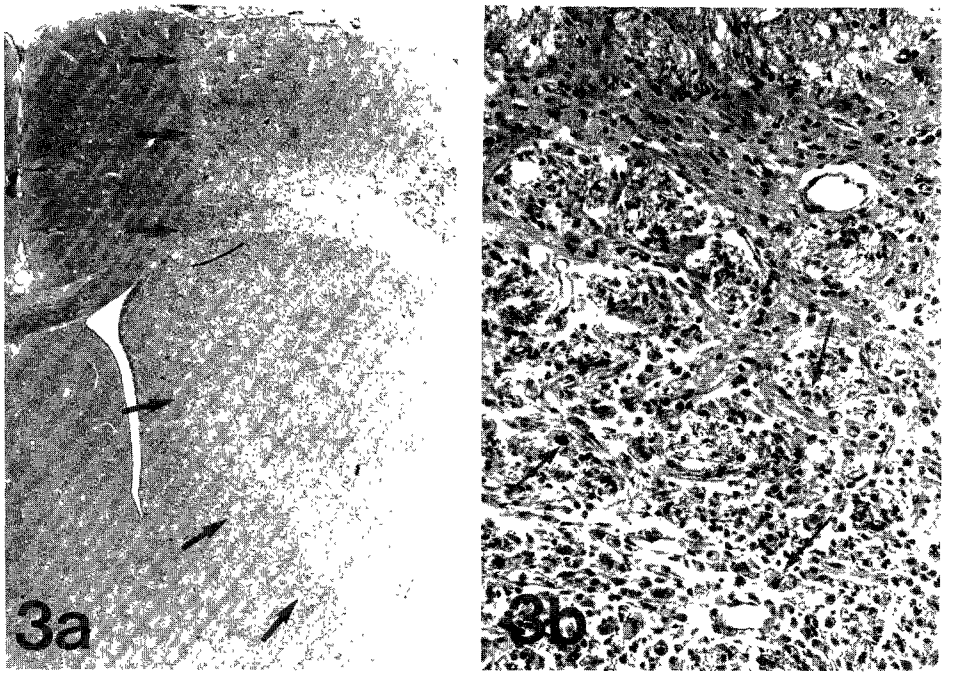


Fig. 3. Infarction involving left cerebral hemisphere.
A : Junction between infaracted area and surrounding tissue is marked by arrows.
(H-E, ×5 original magnification)
B : Gitter cells are noted in the center of the infarction (arrows). (H-E, ×50 original magnification)

volving ipsilateral side of the brain and other 4~5 rats showed severe neuronal damage in anterior and posterior cortex, hippocampus, striatum, and thalamus(Table 2).

With dexamethasone 0.5mg/kg 3 times pretreatment(II), infarction was focal in striatum and thalamus in 3 out of 16 rats(18.7%) (Table 3). Compare to hypoxic-ischemic control group(I), posterior cortex showed more ischemic damage(81.3% vs 62.6 %) even though the infarction was not seen in that area and striatum also showed more damages than control(68.7% vs 56.3%). Anterior cortex, hippocampus, and thalamus showed less damages than control.

With 2.0gm/kg 3 times pretreatment(III), striatum and thalamus showed more infarctions(64.3% and 50% of cases) comapare to hypoxic-ischemic control (I) (31.3%, respectively) and 0.5mg/kg injection group(II) (18.7%, respectively) (Table 4). Anterior

Table 1. Mortality

| Group | Total | Dead | % |
|---|---|---|---|
| I | 33 | 17 | 51.5 |
| II | 28 | 12 | 42.9 |
| III | 32 | 18 | 56.3 |
| IV | 48 | 28 | 58.3 |
| Total | 141 | 75 | 53.2 |

Table 2. Neuronal damages in hypoxic-ischemic control group (without dexamethasone) (n=16)

| Severity of damage | Cortex | | Hippocampus | | | Striatum | Thalamus |
|---|---|---|---|---|---|---|---|
| | Ant | Post | CA3-4 | CA1-2 | Dent | | |
| 3* | 5(31.3) | 5(31.3) | 5(31.3) | 5(31.3) | 5(31.3) | 5(31.3) | 5(31.3) |
| 2 or 3 | 5(31.3) | 5(31.3) | 4(25) | 1(6.3) | 1(6.3) | 4(25) | 5(31.3) |
| 0 or 1 | 6(37.5) | 6(37.5) | 7(43.7) | 10(62.5) | 10(62.5) | 7(43.7) | 6(37.5) |

Ant : anterior
Post : posterior
CA : cornus ammonis
Dent : dentate gyrus
( ) : percentage of cases

Table 3. Neuronal damages in group II (Dexamethasone 0.5mg/kg 3 times pretreatment) (n=16)

| Severity of damage | Cortex | | Hippocampus | | | Striatum | Thalamus |
|---|---|---|---|---|---|---|---|
| | Ant | Post | CA3-4 | CA1-2 | Dent | | |
| 3* | 0 | 0 | 0 | 0 | 0 | 3(18.7) | 3(18.7) |
| 2 or 3 | 9(56.3) | 13(81.3)[1)] | 7(43.7) | 4(25) | 3(18.7) | 8(50)[2)] | 3(18.7)[3)] |
| 0 or 1 | 7(43.7) | 3(18.7) | 9(56.3) | 12(75) | 13(81.3) | 5(31.3) | 10(62.5) |

1) 2 cases : bilateral
2) 4 cases : bilateral
3) 1 case : bilateral

Table 4. Neuronal damages in group III (Dexamethasone 2.0mg/kg 3 times pretreatment) (n=14)

| Severity of damage | Cortex | | Hippocampus | | | Striatum | Thalamus |
|---|---|---|---|---|---|---|---|
| | Ant | Post | CA3-4 | CA1-2 | Dent | | |
| 3* | 1(7.1)[1)] | 3(21.4) | 4(28.6) | 4(28.6) | 3(21.4) | 9(64.3) | 7(50) |
| 2 or 3 | 7(50)[2)] | 8(57.1)[3)] | 3(21.4)[4)] | 3(21.4) | 4(28.6)[5)] | 3(21.4)[6)] | 2(14.3)[7)] |
| 0 or 1 | 6(42.9) | 3(21.4) | 7(50) | 7(50) | 7(50) | 2(14.3) | 5(35.7) |

1) RT : $2^+$
2) 2 cases : bilateral
3) 3 cases : bilateral
4) 3 cases : bilateral
5) 2 cases : bilateral
6) 2 cases : bilateral
7) 1 case : bilateral

Table 5. Neuronal damages in group IV (Dexamethasone 1.0mg/kg 3 times posttreatment) (n=20)

| Severity of damage | Cortex | | Hippocampus | | | Striatum | Thalamus |
|---|---|---|---|---|---|---|---|
| | Ant | Post | CA3-4 | CA1-2 | Dent | | |
| 3* | 4(20) | 4(20) | 6(30) | 6(30) | 5(25) | 10(50) | 6(30) |
| 2 or 3 | 12(60) | 13(65) | 10(50) | 11(55) | 6(30) | 6(30) | 9(45) |
| 0 or 1 | 4(20) | 3(15) | 4(20) | 3(15) | 9(45) | 4(20) | 5(25) |

Table 6. Statistical analysis of results

| Groups | Cortex | | Hippocampus | | | Striatum | Thalamus |
|---|---|---|---|---|---|---|---|
| | Ant | Post | CA3-4 | CA1-2 | Dent | | |
| I, II | | | | | | | |
| I, III | | | | | | | |
| I, IV | | | | <0.01 | | | |
| II, III | | | | | | | |
| II, IV | | | | <0.005 | | | |
| III, IV | | | | | | | |

Ant : anterior
Post : posterior
CA : cornus ammonis
Dent : dentate gyrus

and posterior cortex showed less infarction(7.1% and 21.4%, respectively) than control(31.3%, respectively) but more than 0.5mg/kg group(II) (none). Hippocampus showed similar findings to cortex(21.4~28.6% vs 31.3% and none). Moderate to severe neuronal damage was more common in anterior and posterior cortex of this group(50% and 57.1%, respectively) compare to control(31.3%, respectively) and less common than 0.5mg/kg group(II) (56.3% and 81.3%, respectively).

With 1.0mg/kg 3 times posttreatment(IV), neuronal damage was worst of all groups, showing 20% infarction in anterior and posterior cortex, 25~30% in hippocampus, and 50% and 30% in striatum and thalamus, respectively(Table 5). Only CA1-2 area of hippocampus showed significantly more neuronal damages compare to groups I and II(Table 6).

## Discussion

In rats, anoxia alone does not produce brain damage and Levine[20] described anoxia combined with unilateral common carotid artery occlusion resulted in ischemic alteration in a large proportion of rats. We used Levine's method with some modification to reduce the mortality rate and 31.3% of hypoxic-ischemic control rats showed ipsilateral large infarction and additional 4~5 rats showed severe neuronal damages in various areas(Table 2).

Dexamethasone has multiple mechanism of actions such as modulation of the stress hormones release with control of pituitary-adrenal axis[21] and affects the neurotransmitter metabolism and action [22] and glial glucose metabolism[23]. Previous clinical and experimental studies with glucocorticoid for pre-or posttreatment of focal or global ischemia in adult showed lack of success or negative effects[15-18]. Koide et al[16] administered dexamethasone 2 mg/kg at different timing including chronic pretreatment (2 days, 1 day, and 3 hour before ischemia) and posttreatment (5 min and 6 hour, and 1 day after ischemia), and acute pretreatment (3 hour before ischemia). None of the drugs used, whether given before or after ischemia, affected the outcome, except chronic dexamethasone pretreatment caused a massive increase in neuronal damage.

The deteriolating effect of chronic pretreatment of animals with dexamethasone has been explained by elevated blood glucose and lactic acidosis. Chronic treatment with glucocorticoid elevates the glucagon concentration in plasma and glucagon stimulates gluconeogenesis[24-25]. In addition, chronic dexamethasone treatment not only raised the plasma glucose concentration but also affected glucose transport and metabolism during ischemia, possibly by increasing blood flow and/or enhancing glucose metabolism. Excessive lactic acidosis associated with elevated plasma glucose levels has been known to adversely affect recovery following cerebral ischemia[4)26-29]. This could explain the more deterious effects of incomplete ischemia than complete ischemia in fed or glucose-infused animals[30]. Critical lactic acid concentrations has been known as 15-25 μmol $g^{-1}$ wet brain, but role of other nutritional factors is not fully understood yet.

Corticosteroids also act on glucocorticoid receptors and desensitize the adrenergic β-receptors[31-32]. Blomqvist et al[38] reported protective effect of chronic pretreatment in locus ceruleus system. In addition, chronic dexamethasone treatment could aggravate kainic acid-induced neuronal damage and ischemic damage via excitotoxic mechanisms[15)34].

The present study showed differences between dosages and timing of administration of dexamethasone. Dexamethasone 0.5mg/kg pretreatment produced focal infarction in striatum and thalamus in 18.7%, but more ischemic damage in posterior cortex and striatum. Other areas such as anterior cortex, hippocampus, and thalamus showed less damages than control(Table 3). But overall neuronal damages were not significantly different from control group. With dexamethasone 2.0mg/kg administered at the same time, more infarctions were produced in striatum and thalamus(64.3% and 50% of cases) compare to hypoxic-ischemic control and 0.5mg/kg injection groups(31.3% and 18.7%, respectively). But the changes were vaiable in different areas. For example, infarction was less common in anterior and posterior cortex(7.1% and 21.4%, respectively) than control(31.3%, respectively) and more than 0.5mg/kg injection group(none), but moderate to severe neuronal damages were more common(50% and 57.1%, respectively) than control (31.3%, respectively) and less common than 0.5 mg/kg group(56.3% and 81.3%, respectively). Again, overall brain damages were not significantly different between groups. This experiment could not explain the reason for these differences between dosages and topography, although differences in distribution of receptors for excitatory amino acids (EAAs) could participate in these changes. Further study with larger numbers and receptor determination will be able to explain it better.

Posttreatment of dexamethasone 1.0mg/kg produced worst neuronal damages with infarction in 20~50% of cases in various areas, most common in striatum(50%) and thalamus and cornus ammonis(CA) of hippocampus(30%, respectively) (Table 5). Among these, only CA1-2 area showed significantly more neuronal damages than hypoxic-ischemic control and 0.5mg/kg pretreatment groups($p<0.01$ and $p<0.005$, respectively). This adverse effects of posttreatment of dexamethasone were similar to previous studies and support the current caution against the use of dexamethasone in ischemic disease. The controversal results of previous studies as well as present study are thought to be a results of difference of dosage and administration timing and method(acute or chronic) of glucocorticoid, and used hypoxia-ischemia models.

The effects of glucocorticoid in perinatal period has been studied extensively because glucocorticoids were frequently used both antenatally to prevent respiratory distress syndrome by inducing fetal production of pulmonary surfactant as well as postnatally to improve lung function in infants with bronchopulmonary dysplasia[35-37]. Afterwards, increased risk of cerebral hypoxia-ischemia during or after glucocorticoid administration was reported[38-39]. Also in the model of neonatal hypoxia-ischemia,

adverse effects of glucocorticoids have been well documented[40-41] and glucocorticoid therapy was recently not recommended for treatment of newborn infants with hypoxic-ischemic encephalopathy [42]. Recently, Barks et al[19] demonstrated different response according to administration time of dexamethasone : posttreatment or immediate pretreatment was ineffective in improving the pathology contrast to pretreatment with dexamethasone prevented hypoxic-ischemic brain damage in the neonate. They showed neuroprotective effect of much lower doses of glucocorticoid and latency of action of several hours. The difference in response of dexamathasone administration in adult and immature rats could be explained by various factors involving metabolism of nutrients and other substances, difference in receptors, and other developmental physiologic differences.

In contrast to ishemic disease, corticosteroid is still used for the treatment of acute spinal cord injury and cerebral vasogenic edema. High dose of glucocorticoid can enhance sonsorimotor recovery after blunt spinal cord trauma by at least 3 mechanisms : a facilitation of neuronal excitability and impulse conduction, an improved blood flow, and the preservation of cord ultrastructure through a reduction of injury-induced, free radical-catalyzed lipid peroxidation. Two mechanisms are involved in increased blood flow : 1) potential depression of α-adrenergic receptor sensitivity and enhancement of β-receptor responsiveness in spinal arterioles and 2) interfering the injury-induced activation of prostaglandin system. It is known that 15~30 mg/kg dose of methylprednisolone can prevent spinal cord ischemia when the drug was given at 30 minute after spinal trauma. Glucocorticoid also reduces considerably the vasogenic edema and cell damage possibly by inducing the synthesis of certain proteins with antiphospholipase $A_2$ activity, but has no effects on cytotoxic edema.

## Conclusion

The present study showed no beneficial changes of chronic dexamethasone pretreatment in hypoxic-ischemic adult rat model in contrast to immature rat model, in which chronic pretreatment with same amounts of dexamethasone alleviate neuronal damage. These differences suggest the various physiologic differences between immature and adult rats. Dexamethasone posttreatment aggravated neuronal damages in CA1-2 area of hippocampus compare to hypoxic-ischemic control and pretreatment groups, which confirmed the contraindication of glucocorticoids in ischemic disease.

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= 국문초록 =

## 성숙흰쥐의 허혈－저산소성 병변에서의 덱사메타존의 영향

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급성 척수 손상과 뇌종양 등의 혈관성 부종을 동반하는 질환이 있는 환자에서 당질 코르티코이드를 다량 사용하는 경우 좋은 효과를 보이는 것은 잘 알려져 있고 현재에도 치료의 일환으로 사용되고 있다. 그러나 허혈－저산소성 병변에서는 임상실험이나 실험동물에서 모두 효과가 없거나 오히려 뇌세포의 손상을 악화시키므로 더 이상 사용이 금지되고 있다. 근래에 시행된 한 실험에서 여태까지의 보고들과는 달리 7일 된 미성숙쥐에서 허혈－저산소성 병변이 일어나기 전에 덱사메타존을 여러 번으로 나눠서 투여하는 경우 뇌세포의 손상을 적게 하는 것이 관찰되었고 이러한 소견은 임상에서 미성숙아에서 폐의 기능을 증가시키기 위해 출생 전후에 덱사메타존의 투여를 시도하므로 중요한 의미를 갖는다. 본 실험에서는 덱사메타존을 투여방법과 용량을 다르게 투여하여 그에 따른 뇌세포의 손상을 관찰하였다. 덱사메타존 0.5 mg/kg와 2.0mg/kg를 3회 전처치한 실험동물군이나 1.0mg/kg를 3회 후처치군에서 신경세포의 손상에 의미있는 차이가 없었으며 단지 후처치군에서 해마의 일부에서 다른 군보다 더 심한 손상을 보였다. 이러한 실험결과는 미성숙쥐와 성숙쥐에서 발생하는 허혈－저산소성 병변은 그 기전이나 병변에 관여하는 여러가지 요소가 다른 것을 의미하고 그러한 요소들에 대한 앞으로의 연구가 필수적이라고 생각된다. 또한 허혈－저산소성 병변에서 당질 코르티코이드의 사용이 금지되어야 하는 것을 뒷받침한다.