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Facilitation of ischemia-induced release of dopamine and neuronal damage by dexamethasone in the rat striatum

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Abstract

Glucocorticoids have been reported to aggravate ischemia-induced neuronal damage in both humans and experimental animals. Because an excess release of neurotransmitters is closely related to the outcome of ischemic neuronal damage, we evaluated the effects of dexamethasone on monoaminergic release and histological outcome. Changes in the extracellular concentrations of monoamines and their metabolites in the striatum produced by occlusion of the middle cerebral artery for 20 min were measured using a microdialysis high-performance liquid chromatography procedure, and the effects of intracerebroventricular administration of dexamethasone (10 μg) were evaluated in halothane-anesthesized rats. The histological outcome was evaluated by light microscopy 7 days after ischemia. Additionally, the effects of lesioning of the substantia nigra were estimated. The extracellular concentrations of neither dopamine nor serotonin were affected by the administration of dexamethasone in the nonischemic state. The occlusion of the middle cerebral artery produced a marked increase in the extracellular concentration of dopamine in the striatum, the peak value being 240 times that before ischemia. The preischemic administration of dexamethasone enhanced the increase in dopamine level during ischemia, and the peak value in the dexamethasone group was 640% of that in the vehicle group. After 7 days, ischemic neuronal damage in the dexamethasone group was severe compared with that in the vehicle group. In rats receiving the substantia nigra lesion, the ischemic release of dopamine was abolished, and the aggravation of ischemic neuronal damage by dexamethasone was completely alleviated. Changes in the release of monoamines may be a contributing factor in the development of the ischemic neuronal damage induced by glucocorticoids.

Keywords: Cerebral ischemia; Dexamethasone; Dopamine; Substantia nigra, rat

1. Introduction

The administration of glucocorticoids has been reported to aggravate ischemic brain damage (Sapolosky and Pulsinelli, 1985; Grafton and Longstreth, 1988), although cerebral edema and traumatic injury of the spinal cord improve with these agents. The increase in the plasma concentration of endogenous glucocorticoids, which occurs in stress conditions, also seems to have deleterious effects because ischemic neuronal damage is improved by the inhibition of the synthesis of endogenous glucocorticoids (Smith-Swintosky et al., 1996; Adachi et al., 1999). In cerebral ischemia, various kinds of neurotransmitters (both excitatory and inhibitory) are released from nerve endings (Globus et al., 1988; Hillered et al., 1989; Baker et al., 1991). Excitatory neurotransmitters excessively stimulate the synaptic membrane and lead to irreversible neuronal injury (Rothman and Olney, 1995; Hattori et al., 1998). In contrast, inhibitory neurotransmitters or neuromodulators are thought to provide benefit (Prehn et al., 1993; Nikata et al., 1992). However, treatment with glucocorticoids has been reported to provoke mental disorders such as insomnia and psychopathies of the manic–depressive or schizophrenic type (Steckler and Holsboer, 1999). The pathogenesis of these psychological disturbances may be closely related to changes in the monoaminergic system in the central nervous system because treatment with glucocorticoids has been shown to increase monoamine turnover in the central dopaminergic system (Tsubota et al., 1999). In

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the current study, we evaluated the effect of dexamethasone, a pure glucocorticoid, on the ischemic release of monoamines in the rat striatum, using an animal model of middle cerebral artery occlusion. To clarify the relationship between ischemic monoamine release and histological outcome, the effects of lesioning of the nigrostriatal pathway on these changes were evaluated.

2. Materials and methods

2.1. Animals

This study was approved by the Committee on Animal Experimentation at Ehime University School of Medicine, Ehime, Japan. Male Wistar rats (Charles River, Yokohama, Japan), weighing approximately 280 g at the time of operation, were housed in groups in a temperature-controlled room at 23 ± 2 °C and maintained under an alternating 12-h light/12-h dark cycle (lights on at 6:00 a.m.). Animals were deprived of food for at least 6 h before ischemia was induced because hyperglycemia can influence ischemic brain damage (Ginsberg et al., 1980; Pulsinelli et al., 1982; D'Alecy et al., 1986; Woo et al., 1988). In experiment 1, 20 rats were used to evaluate the effects of intracerebroventricular administration of dexamethasone on monoamine release in the absence of cerebral ischemia. In experiment 2, 22 rats were subjected to cerebral ischemia and changes in the ischemic release of monoamines were examined. In these animals, the histological outcome was evaluated after 7 days. In experiment 3, 15 rats were used to evaluate physiological variables.

2.2. Experiment 1: effects of dexamethasone on monoamine levels

Changes in the extracellular concentrations of monoamines and their metabolites induced by dexamethasone were examined in the nonischemic state. Twenty rats were prepared and assigned to the vehicle and dexamethasone groups (10 animals in each). Rats were anesthesized with 2% halothane in balanced 50% oxygen and 50% nitrous oxide, and they breathed spontaneously. After the animal was placed in a stereotaxic apparatus (Narishige Scientific, Tokyo, Japan) in the prone position, the skull was exposed and two burr holes were drilled: one in the left hemisphere (0.8 mm posterior and 1.5 mm lateral to the bregma) for drug administration, and the other in the right hemisphere (0.3 mm posterior and 4.0 mm lateral to the bregma) for insertion of a microdialysis probe. Then, an I-shaped microdialysis probe (A-I-8-01; Eicom, Kyoto, Japan) was inserted into the right striatum through the burr hole, and its tip was positioned 7.0 mm below the skull. After implantation of the microdialysis probe, the concentration of halothane was reduced to 1.5%, and Ringer's solution (Na^+, 147 mmol/l; K^+, 4 mmol/l; Ca^{2+}, 2 mmol/l; Cl^-, 155 mmol/l) was perfused at a rate of 2 μl/min (KD Scientific, Boston, MA, USA). After a 1-h stabilization period, brain perfusates were collected every 20 min into microtubes on ice and stored at − 80 °C until analysis. After the collection of three samples, 10 μg of water-soluble dexamethasone (cyclodextrin-encapsulated dexamethasone; Sigma, St. Louis, MO, USA) or 168 μg of vehicle (2-hydroxy propyl-β-cyclodextrin; Sigma) was administered into the left lateral ventricle through the burr hole. The drug was given in a constant volume of 20 μl via a 27-gauge needle at a depth of 5 mm below the brain surface. Six samples were collected after vehicle or drug administration. During the experimental period, the rectal temperature was maintained at 37.5 ± 0.2 °C with a heating lamp.

The concentrations of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) in dialysates were determined. The sample was diluted with 0.02 mol/l acetic acid and applied to a high-performance liquid chromatography system with electrochemical detection (Eicom). The system was composed of a pump equipped with a damper (EP-300; Eicom), an electrochemical detector (ECD-300; Eicom) with a graphite working electrode (WE-3G; Eicom) operated at 750 mV versus a silver–silver chloride electrode (RE-100; Eicom), and a reverse-phase column (MA-5ODS, 2.1×150 mm inside diameter; Eicom). The mobile phase was 0.1 mol/l citrate–0.1 mol/l sodium acetate buffer (pH 3.9) containing 13% methanol, 1.0 mmol/l sodium 1-octanesulfonate, and 10 μmol/l of disodium ethylenediaminetetraacetic acid, and the flow rate was 0.23 ml/min.

2.3. Experiment 2: effects of dexamethasone on ischemic release of monoamines

Changes in the ischemic release of monoamines induced by dexamethasone were evaluated in an animal model of middle cerebral artery occlusion. Twenty-two rats were prepared and assigned to the three groups. Animals in the vehicle-injected control group ($n = 8$) were subjected to transient middle cerebral artery occlusion after intracerebroventricular administration of vehicle (20 μl). Animals in the dexamethasone group ($n = 8$) were intra cerebroventricularly injected with dexamethasone (10 μg) before middle cerebral artery occlusion. The effects of lesioning of the substantia nigra were evaluated in dexamethasone-treated rats subjected to middle cerebral artery occlusion ($n = 6$).

In rats with the substantia nigra lesion, bilateral substantia nigra lesions were made 2 days before middle cerebral artery occlusion by stereotaxic injection of 15 μg of 6-hydroxydopamine hydrobromide (dissolved in 5 μl of saline; Research Biochemicals International, Natick, MA, USA) into each substantia nigra, at coordinates of 5.8 mm posterior and 2.0 mm lateral to bregma and 9.0 mm below the skull surface.

We used the middle cerebral artery occlusion model described by Koizumi et al. (1986). After anesthesia with halothane and nitrous oxide, the vehicle (20 μl) or dexamethasone (10 μg) was stereotaxically administered in a procedure identical to that described in experiment 1. The microdialysis probe was inserted into the right striatum and fixed on the skull with dental cement. The probe was perfused with Ringer's solution at 2 μl/min, and brain perfusates were collected every 20 min. With the rats in a supine position, the skin was incised along the median line of the neck, and the right carotid artery was exposed. The rectal and temporal muscle temperatures were maintained carefully at 37.5 ± 0.2 °C, using heating lamps, during the experiment (Busto et al., 1987). The root of the right middle cerebral artery was occluded by insertion of a 4-0 nylon thread from the bifurcation of the internal and external carotid arteries. The 8-mm tip portion of this thread was coated with silicone to render its diameter 0.30–0.34 mm. The tip of the thread was placed 16.5 mm distal from the bifurcation. After 20 min of ischemia, the threads were pulled by 5 mm to restore the blood flow. Three fractions before ischemia, one fraction during ischemia, and six fractions after reperfusion were collected. After removal of the probes, all surgical incisions were sutured. The animals were allowed to recover from anesthesia; the rectal temperature was kept at 37–38 °C. The animals were then brought to their cages in a room maintained at constant temperature and allowed access to food and water ad libitum.

Seven days after this transient forebrain ischemia, the animals were anesthesized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg). The brains were perfused with heparinized saline and fixed with 10% buffered formalin. Then, the brains were dissected. After dehydration with graded concentrations of alcohol solutions, the brains were embedded in paraffin. Brain slices, 4 μm thick, were stained with hematoxylin and eosin. The number of preserved neurons in the striatum and cerebral cortex per 1 mm^2 area on each hemisphere was counted in the coronal section at the level of the optic chiasm in a single blinded manner.

2.4. Experiment 3: measurements of physiological variables

Another group of 15 rats was prepared to determine the physiological variables that may influence the extent of the

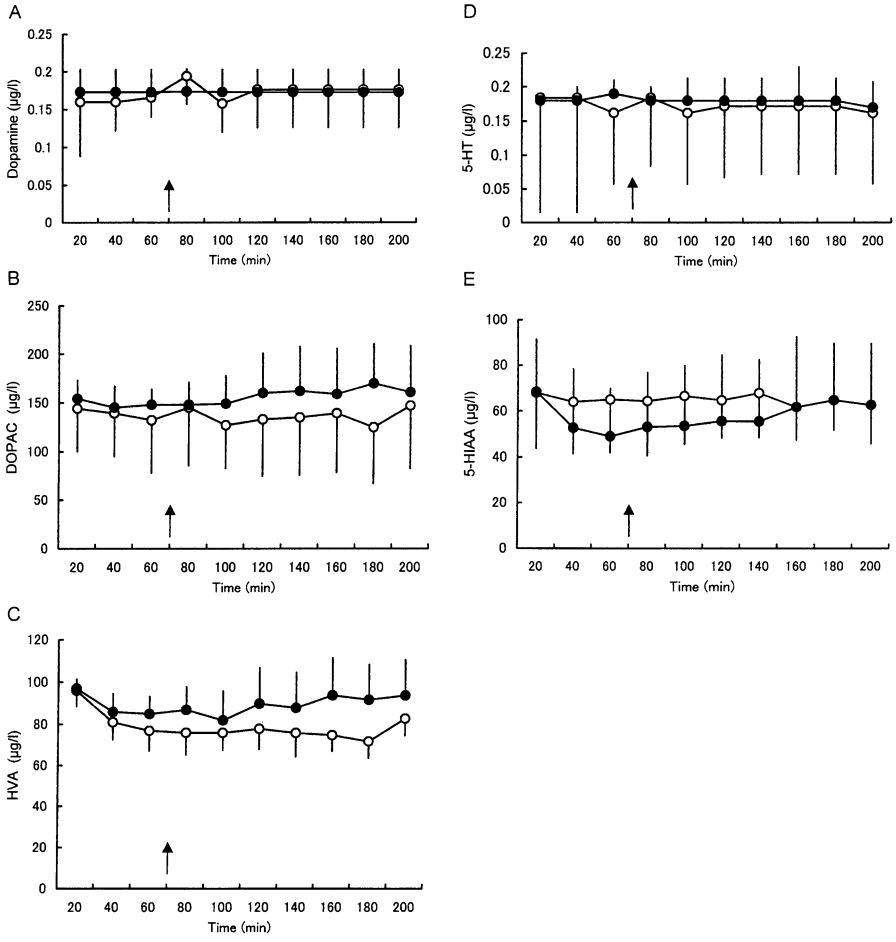

Fig. 1. Effects of dexamethasone on the concentrations of dopamine (A), DOPAC (B), HVA (C), 5-HT (D), and 5-HIAA (E) in dialysates from the striatum. Vehicle-injected group (○) and dexamethasone-injected group (10 μg, intracerebroventricular) (●). Arrows represent the administration of vehicle or dexamethasone. Each value represents the mean ± S.D. for 10 animals.

neuronal damage caused by ischemia. The animal was anesthesized with halothane and nitrous oxide. Five animals with the substantia nigra lesion were given dexamethasone (10 μg) intracerebroventricularly. Ten animals without the substantia nigra lesion were given dexamethasone (10 μg) or vehicle ($n = 5$ each). With the animal in a supine position, the common carotid artery was exposed, and a 22-gauge Teflon catheter was inserted into the artery to monitor the blood pressure, using a model AP-641G blood pressure amplifier (Nihon Kohden, Tokyo, Japan). Two hours after the drug was administered, a blood sample was collected through the catheter to measure plasma glucose, electrolytes, and arterial blood gas levels according to routine laboratory procedures (blood glucose testing system by electrode, MPG01; Daikin, Osaka, Japan; ABL 505; Radiometer, Copenhagen, Denmark). During the experiment, the rectal temperature was maintained at 37–38 °C.

2.5. Statistical analysis

The data from the microdialysis experiments were analyzed using repeated-measures analysis of variance to detect differences between groups. When differences were found, the Bonferroni test was used post hoc to compare each fractional value with that in the corresponding vehicle group. The data for histological and physiological variables

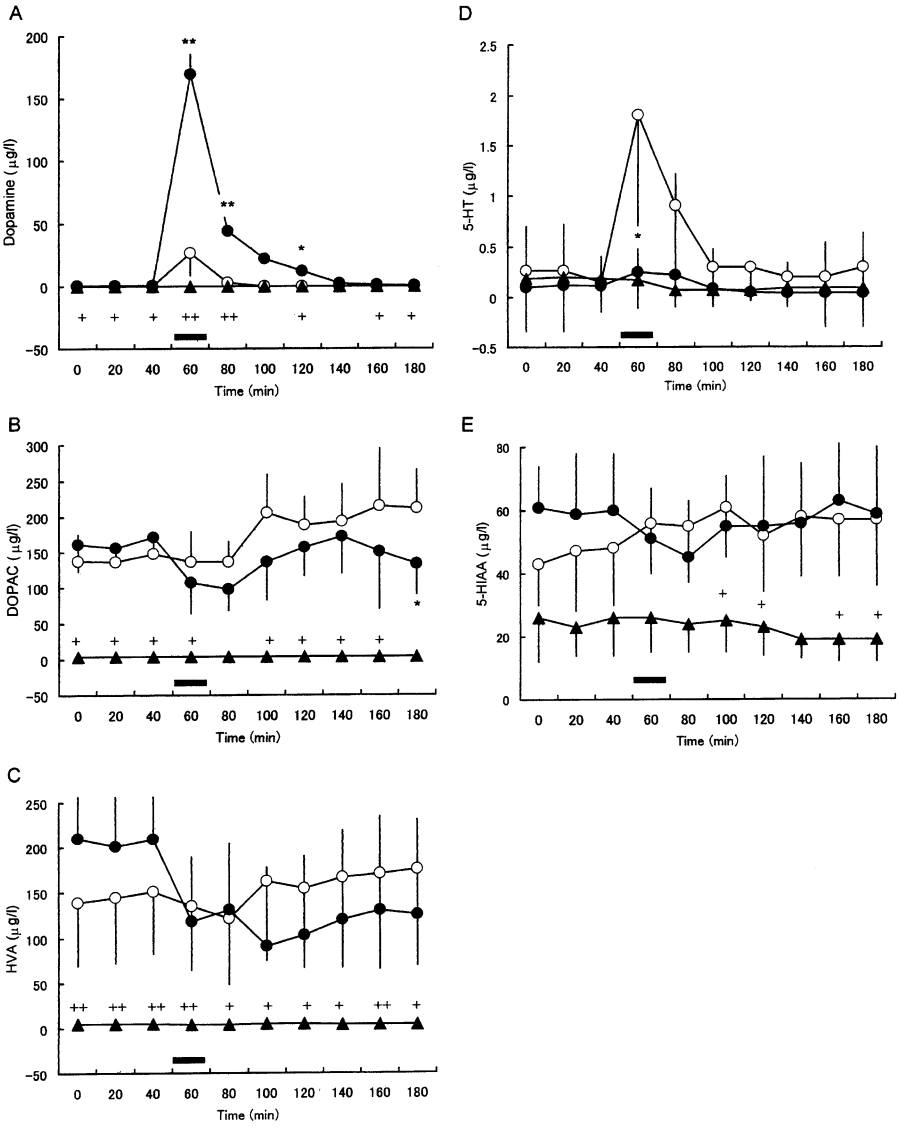

Fig. 2. Effects of dexamethasone on ischemic changes in the concentrations of dopamine (A), DOPAC (B), HVA (C), 5-HT (D), and 5-HIAA (E) in dialysates from the striatum. Solid rectangles designate the duration of ischemia (20 min) produced by occlusion of the middle cerebral artery. Vehicle-injected group ($n = 8$) (○), dexamethasone-injected group (10 μg, intracerebroventricular; $n = 8$) (●), and dexamethasone-injected group with the substantia nigra lesion ($n = 6$) (▲). Each value represents the mean ± S.D. *$P < 0.05$, **$P < 0.01$ as compared with each corresponding value in the vehicle group. $^{+}P < 0.05$, $^{++}P < 0.01$ as compared with each corresponding value in the dexamethasone group.

were analyzed using analysis of variance with the Bonferroni test.

3. Results

3.1. Monoamine levels in the nonischemic state

The intracerebroventricular administration of dexamethasone did not affect the concentrations of dopamine, DOPAC, and HVA in dialysates in the nonischemic state. The values were almost constant during the experimental period, and there were no differences in values between the dexamethasone and vehicle groups (Fig. 1A–C). Likewise, there were no differences in the concentrations of 5-HT and 5-HIAA between the dexamethasone and vehicle groups (Fig. 1D and E).

3.2. Monoamine levels in the ischemic state

The concentration of dopamine in dialysates did not differ between the dexamethasone and vehicle groups before induction of ischemia (Fig. 2A). Cerebral artery occlusion produced a marked increase in the dopamine level, with the peak value being 240 times that before ischemia. The value returned to the basal level immediately after reperfusion. The preischemic administration of dexamethasone enhanced the increase in the dopamine level during ischemia, and the peak value in the dexamethasone group was 640% of that in the vehicle group. The recovery of the dopamine level after reperfusion in the dexamethasone group was later than that in the vehicle group, with the basal level being reached 1 h after reperfusion. There were no remarkable differences in the concentrations of DOPAC and HVA between the two groups throughout the experimental period (Fig. 2B and C). The substantia nigra lesion induced by the injection of 6-hydroxydopamine abolished the output of both dopamine and its metabolites in dialysates. Additionally, the ischemic increase in the dopamine level was completely inhibited by the substantia nigra lesion.

The concentration of 5-HT in dialysates did not differ between the dexamethasone and vehicle groups before the induction of ischemia (Fig. 2D). Transient ischemia for 20 min produced a significant increase in 5-HT concentrations in the vehicle group. The presence of dexamethasone completely suppressed the increase. There were no remarkable changes in the 5-HIAA level between the vehicle and dexamethasone groups (Fig. 2E). The 5-HIAA level was suppressed by the substantia nigra lesion, although the extent of suppression was smaller than that for the dopamine metabolites.

All animals regained consciousness and the righting reflex within 30 min after halothane anesthesia was stopped. No seizures were noted in any animals in the 7-day period between ischemia and death. In rats with the substantia nigra lesion, spontaneous activity was reduced compared with that of the animals in the other two groups.

3.3. Histological outcome

On histological evaluation 7 days after ischemia, the number of striatal neurons in the control group was reduced to 57% of that on the nonischemic side (Fig. 3). The treatment with dexamethasone did not affect the number of neurons on the nonischemic side. However, dexamethasone aggravated the ischemic damage, and the number of preserved neurons in the dexamethasone group was 8% of that on the nonischemic side. Likewise, the ischemic damage in the cerebral cortex was aggravated by the dexamethasone treatment. The magnitude of the deleterious effect was greater in the striatum than in the cerebral cortex. The substantia nigra lesion induced by 6-hydroxydopamine alleviated the aggravation of ischemic neuronal damage

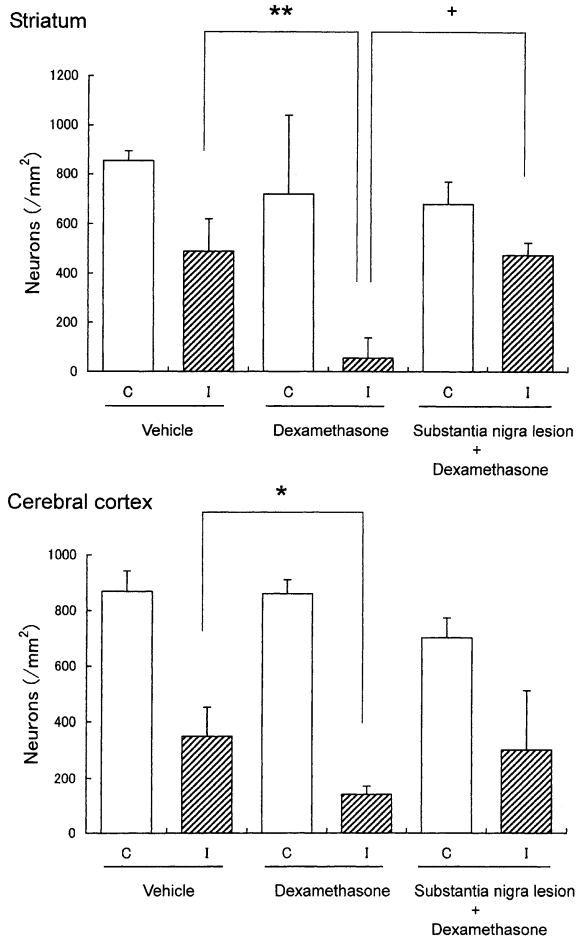

Fig. 3. Effects of preischemic administration of dexamethasone (10 μg, intracerebroventricular) on ischemic neuronal damage in the striatum and cerebral cortex. The number of preserved neurons (/mm^2) was counted 7 days after transient middle cerebral artery occlusion for 20 min. Contralateral side (C) and ipsilateral side (I). *$P<0.05$, **$P<0.01$ as compared with each corresponding value in the vehicle group. $^{+}P<0.01$ as compared with each corresponding value in the dexamethasone group.

Table 1
Physiological variables

	Vehicle	Dexamethasone	Substantia nigra lesion + dexamethasone
Systolic blood pressure (mm Hg)	100 ± 14	100 ± 13	96 ± 17
Diastolic blood pressure (mm Hg)	76 ± 14	79 ± 4	66 ± 5*
Arterial blood gas analysis			
pH	7.439 ± 0.035	7.423 ± 0.058	7.483 ± 0.017
pCO_2 (mm Hg)	39.2 ± 3.0	40.1 ± 3.3	39.2 ± 4.2
pO_2 (mm Hg)	115.6 ± 39.9	113.1 ± 26.6	118.5 ± 15.1
HCO_3^- (mmol/l)	25.6 ± 0.5	26.0 ± 1.8	20.5 ± 10.4
Base excess (mmol/l)	1.0 ± 1.5	2.2 ± 2.2	1.5 ± 2.2
Na^+ (mmol/l)	139 ± 2	138 ± 1	139 ± 3
K^+ (mmol/l)	3.4 ± 0.3	3.3 ± 0.5	3.5 ± 0.4
Ca^{2+} (mmol/l)	1.24 ± 0.03	1.20 ± 0.09	1.14 ± 0.10
Glucose (mg/dl)	149 ± 16	129 ± 14	132 ± 24

Dexamethasone (10 μg) was administered intracerebroventricularly under anesthesia, and physiological variables were determined 2 h after the start of the administration. Control animals were administered cyclodextrin. Each value represents the mean ± S.D. for five animals. *$P<0.05$ as compared with the value in the dexamethasone group.

produced by dexamethasone in the striatum, and the number of preserved neurons in the substantia nigra lesion group was 70% of that on the nonischemic side. In the cerebral cortex, the substantia nigra lesion tended to improve the ischemic damage produced by dexamethasone, although the effect was not significant.

3.4. Physiological variables

Diastolic blood pressure in the substantia nigra lesion group was lower than that in the other groups (Table 1). There were no differences in the other physiological variables among the three groups.

4. Discussion

In this study, dexamethasone facilitated the ischemic release of dopamine and suppressed that of 5-HT, although the agent did not affect the extracellular concentrations of either monoamines in the nonischemic state. The agent aggravated ischemic neuronal damage in both the striatum and the cerebral cortex, and the magnitude of damage was greater in the striatum than in the cerebral cortex. The depletion of striatal dopamine alleviated the ischemic damage in the striatum. These findings indicate that dexamethasone aggravates ischemic neuronal damage by facilitating the release of dopamine in the striatum.

Since changes in brain monoamine levels following cerebral ischemia were first reported by Zervas et al. (1974), many investigators have shown abnormalities in brain monoamine metabolism in various animal models of cerebral ischemia (Wurtman and Zervas, 1974; Solomon et al., 1986). With respect to the effect of dopamine on ischemic neuronal damage, there are several reports that suggest detrimental effects of dopamine in cerebral ischemia. The depletion of striatal dopamine produced by a lesion of the substantia nigra has been reported to protect striatal neurons from ischemic damage (Clemens and Phebus, 1988; Globus et al., 1987). Although the mechanism by which dopamine exacerbates neuronal damage in ischemia is unclear, similar phenomena were observed in the present study. Because the substantia nigra lesion alleviated the aggravation of ischemic damage induced by dexamethasone, the observed enhancement of the ischemia-induced increase in the extracellular concentration of dopamine is strongly suggested to be related to the aggravation of morphological changes in the striatum.

The severe damage in the striatum in dexamethasone-treated rats may have been due to the difference in innervation between the striatum and the cerebral cortex. Since neurons in the striatum are predominantly innervated by dopaminergic fibers, the aggravation may be marked in the striatum due to the enhanced release of dopamine. In our previous studies, dexamethasone facilitated the ischemic release of glutamate in the hippocampal CA1 area, and aggravated ischemic neuronal damage in this region (Chen et al., 1998). This suggests an enhancement of the excitotoxicity of glutamate by dexamethasone in the hippocampal CA1 area, where glutamatergic fibers are distributed from cell bodies present in the CA3 area. Although both the striatum and the cerebral cortex are innervated by glutamatergic fibers, additional effects of dopamine may have caused the severe aggravation of damage in the striatum. In the present study, the substantia nigra lesion tended to alleviate the aggravation of damage in the cerebral cortex as well as in the striatum, although the extent of the alleviation was not significant. The reason why the alleviation was not limited in the striatum is unclear. Indirect effects of lesioning the nigrostriatal pathway might have affected the outcome in the cerebral cortex by changing the density of cortical innervation.

Two subtypes of dopamine receptors have been shown to play different roles in ischemic neuronal damage. A facilitatory effect on ischemia-induced neuronal deficits by dopamine D1 receptor stimulation has been reported in rat hippocampal slices (Yamamoto et al., 1994), whereas dopamine D2 receptor activation is indicated to be neuroprotective against ischemic brain injury in a gerbil model of cerebral ischemia (O'Neill et al., 1998). Because the depletion of dopamine prior to ischemia is beneficial against ischemic damage, simultaneous stimulation of both dopamine D1 and D2 receptors may have deleterious effects. The detrimental effects of dopamine D1 receptor activation seem to be stronger than the protective effects of dopamine D2 receptor activation. In rats subjected to the substantia nigra lesion, diastolic blood pressure was decreased. This seems

to be due to a reduction of vascular resistance. Hypotension usually aggravates ischemic or hypoxic brain injury. Considering the lack of injury aggravation in the substantia nigra-lesioned rats despite hypotension, it is unlikely that hypotension is a factor in the morphological outcome.

The increase in dopamine oxidation by monoamine oxidase is considered to be an important mechanism for dopamine toxicity as well as its action through specific receptors (Hyslop et al., 1995) because dopamine oxidation during ischemia and reperfusion generates reactive oxygen species. Two possible processes have been hypothesized as being responsible for the production of reactive oxygen species: one is the oxidation of dopamine by monoamine oxidase to produce hydrogen peroxide and DOPAC (Marker et al., 1981), and the other is the spontaneous and enzymatic oxidation of the catechol ring to form hydrogen peroxide (Hastings, 1995). Although dexamethasone increased neither the DOPAC level nor the HVA level in the present study, the total effect of dopamine release may contribute to the aggravation of ischemic damage.

Two mechanisms for dopamine release have been suggested from an in vitro study with brain slices (Kim et al., 1995). One is the rapid Ca^{2+}-dependent exocytolic release of dopamine from synaptic vesicles on depolarization of the plasma membrane as a neurotransmitter; the other is the efflux caused by the reversal of transporters in a Ca^{2+}-independent manner. In the present study, dexamethasone facilitated the ischemic release of dopamine, whereas it did not affect the extracellular dopamine level in the nonischemic state. Because dopamine is released in both manners in cerebral ischemia (Kim et al., 1995), glucocorticoids seem to facilitate mainly Ca^{2+}-independent dopamine release. The enhancement of dopamine release in ischemia in dexamethasone-treated animals may be caused by the facilitation of Ca^{2+}-independent release. In our previous studies, dexamethasone dose-dependently suppressed Na^+, K^+-ATPase activity under acidic conditions (Adachi et al., 2001; Namba et al., 2002). Because inhibition of Na^+, K^+-ATPase by ouabain has been shown to result in reversal of the uptake process of dopamine and in Ca^{2+}-independent release (Milusheva et al., 1996), suppression of Na^+, K^+-ATPase activity by dexamethasone may be a mechanism responsible for the facilitation of the ischemic increase in the extracellular dopamine level.

Concerning the effect of dexamethasone on the serotonergic system, the agent suppressed the ischemic increase in the extracellular concentration of 5-HT. This may reflect the decrease in the ischemic release of 5-HT, facilitation of reuptake, or degradation associated with a decreased synthesis. Although the details of the changes in dopamine and 5-HT release were not elucidated in the present study, dexamethasone seems to suppress the ischemic release of 5-HT and to facilitate that of dopamine. There is a study that suggests that increased activity of the serotonergic system has a beneficial effect on the ischemic brain (Nikata et al., 1992). The increase in the 5-HT concentration in the synaptic cleft resulting from the blockade of the reuptake mechanism has been shown to be neuroprotective against cerebral ischemia, whereas the depletion of 5-HT from the neuron has been reported to aggravate ischemic neuronal injury (Oishi et al., 1989; Prehn et al., 1993). Further, 5-HT1A receptor agonists can reduce neuronal injury by inhibiting the release of glutamate (Prehn et al., 1993; Reynolds and Miller, 1988; Maura et al., 1988). Therefore, the exacerbation of the histological outcome by glucocorticoids may be partly caused by the inhibition of serotonergic activity.

In the present study, lesioning of the nigrostriatal pathway reduced the 5-HIAA level. Because the substantia nigra lesion has been reported to induce a reduction in striatal innervation density (Takeuchi et al., 1991), the decrease in the 5-HIAA level may be attributed to a decrease in serotonergic innervation. Despite the suppression of serotonergic activity, beneficial effects were observed after disruption of the dopaminergic innervation. These findings suggest that the deleterious effects of dopaminergic facilitation are greater than the beneficial effects of serotonergic facilitation.

In conclusion, dexamethasone enhances the ischemic release of dopamine and suppresses that of 5-HT, and we speculate that these responses may be contributing factors in the aggravation of ischemic neuronal damage induced by glucocorticoids.

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