Animal Cells and Systems
Vol. 15, No. 4, December 2011, 279–286

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Hypothermia alleviates hypoxic ischemia-induced dopamine dysfunction and memory impairment in rats

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(*Received 29 March 2011; received in revised form 17 June 2011; accepted 23 June 2011*)

Hypoxic ischemia injury is a common cause of functional brain damage, resulting from a decrease in cerebral blood flow and oxygen supply to the brain. The main problems associated with hypoxic ischemia to the brain are memory impairment and dopamine dysfunction. Hypothermia has been suggested to ameliorate the neurological impairment induced by various brain insults. In this study, we investigated the effects of hypothermia on memory function and dopamine synthesis following hypoxic ischemia to the brain in rats. For this purpose, a step-down avoidance task, a radial eight-arm maze task, and immunohistochemistry for tyrosine hydroxylase (TH) and 5-bromo-2′-deoxyuridine (BrdU) were performed. The present results indicated that the hypoxic ischemia-induced disturbance of the animal's performances and spatial working memory was associated with a decrement in TH expression in the substantia nigra and striatum, and an increase in cell proliferation in the hippocampal dentate gyrus. Hypothermia treatment improved the animals' performance and spatial working memory by suppressing the decrement in TH expression in the substantia nigra and striatum and the increase in cell proliferation in the dentate gyrus. We suggest that hypothermia can be an efficient therapeutic modality to facilitate recovery following hypoxic ischemia injury to the brain, presumably by modulating the dopaminergic cell loss.

Keywords: hypoxic ischemia; hypothermia; dopamine; memory; cell proliferation

Introduction

Hypoxic ischemia injury is a common cause of functional brain damage, resulting from a decrease in cerebral blood flow and oxygen supply to the brain, and induces a decline in memory function. Hypoxic ischemia injures multiple brain regions, including substantia nigra (SN), basal ganglia, striatum, and hippocampus, resulting in neurological damage and cognitive impairments (Fan et al. 2006).

Decreased memory function is associated with changes in neurotransmitters such as dopamine, serotonin, adrenaline, and acetylcholine. Of these, dopamine, one of the major catecholamines in the central nervous system, is crucial for memory function (Li et al. 2010). The dopamine system contributes to the control of motor activity, behavior, and cognition. Dopamine dysfunction is involved in a variety of neurological disorders, such as Parkinson's disease (Filippi et al. 2010). Presynaptic biochemical markers of dopamine reuptake are relatively spared in the unilateral hypoxic ischemia model. In particular, recovery of the nigrostriatal dopaminergic pathway is associated with the appearance of tyrosine hydroxylase (TH)-positive cells after focal ischemia (Yanagisawa et al. 2006).

TH is the rate-limiting enzyme in the synthesis of catecholamine neurotransmitters such as dopamine, epinephrine, and norepinephrine. More specifically, it converts L-tyrosine to L-dihydroxyphenylalanine (L-DOPA), which is rate-limiting in dopamine synthesis (Asanuma et al. 2003). TH activity is progressively decreased with the loss of dopamine neurons in the SN of Parkinson's disease patients. Thus, TH immunohistochemistry is widely used to detect the injury or death of dopaminergic fibers and cell bodies (Hurley et al. 2004).

The hippocampus is critically involved in learning ability and memory function. The dentate gyrus in the hippocampus is a brain region in which neurogenesis occurs in adult mammals (Gould et al. 1999; Gage 2002). The newly generated neurons participate in the storage of hippocampus-dependent memory (Gould

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ISSN 1976-8354 print/ISSN 2151-2485 online

http://dx.doi.org/10.1080/19768354.2011.607514
http://www.tandfonline.com

et al. 1999). Previous studies have shown that the proliferation of granular cell precursors and neurogenesis in the adult hippocampal dentate gyrus are enhanced by estrogen, *N*-methyl-D-aspartate receptor antagonists, seizure, ischemia, and ATP consumption, whereas adrenal steroids, stress, and aging reduce new cell formation (Gould et al. 1999; Gage 2002; Lee et al. 2002; Kim et al. 2004).

Hypothermia, as a medical treatment, is a lowering of body temperature to reduce the risk of ischemic injury to tissues following a period of insufficient blood flow (Thoresen et al. 2009). Mild therapeutic hypothermia is being increasingly used for patients suffering from cardiac arrest. Clinical reports have indicated that mild hypothermia reduces brain edema from stroke and traumatic brain injury (Losiniecki and Shutter 2010). Hypothermia treatment has also been used to prevent apoptosis, reduce cerebral oxygen consumption, mitigate reperfusion injury, suppress reactive oxygen species, and inhibit the release of various neurotransmitters (Grocott 2009). Although clinical benefits of hypothermia treatment for various injuries have been widely reported, the exact mechanisms underlying these neuroprotective effects are still unclear.

In this study, we investigated the effects of hypothermia on memory function (the animals' performance and spatial working memory) in relation to the dopaminergic system following hypoxic ischemia in rats. For this purpose, we performed a step-down avoidance task for short-term memory and a radial eight-arm maze task for spatial-learning memory. TH immunohistochemistry for the integrity of dopaminergic system in the SN and striatum and 5-bromo-2′-deoxyuridine (BrdU) immunohistochemistry for cell proliferation in the dentate gyrus of the hippocampus were also conducted.

Materials and methods

Experimental animals

Adult male Sprague-Dawley rats weighing 180 ± 5 g (6 weeks of age) were obtained from a commercial breeder (Orient Co., Seoul, Korea). Experimental procedures were performed in accordance with the animal care guidelines of the National Institutes of Health and the Korean Academy of Medical Sciences. Each animal was housed under controlled temperature ($22 \pm 2^{\circ}$C) and lighting (08:00–20:00) conditions with food and water available ad libitum before and after surgery.

The animals were randomly divided into four groups ($n = 10$ in each group): a sham-operation group, a hypoxic ischemia group, a hypoxic ischemia and hyperthermia group, and a hypoxic ischemia and hypothermia group.

Induction of hypoxic ischemia injury and treatments

The surgical procedure and treatment protocols were performed as previously described (Alva et al. 2010). In brief, rats were anesthetized with isoflurane (2% isoflurane in 30% O_2 and 70% N_2; Vibac Laboratories, Carros, France). Following bilateral neck incision, both common carotid arteries were exposed and occluded with aneurysm clips for 2 h. All rats were placed in a chamber with humidified 8% O_2 and 92% N_2 for 2 h at 37°C. After 2 h of hypoxic ischemia injury, all rats received 50 mg/kg BrdU (Sigma-Aldrich Co., St. Louis, MO, USA) intraperitoneally. Then the rats in the hypoxic ischemia group were placed in room cases at 22°C, the rats in the hypoxic ischemia and hyperthermia group were placed in an incubator at 35°C, and the rats in the hypoxic ischemia and hypothermia group were placed in a cold room at 4°C, for 3 h depending on the respective treatment regimen. After that, all rats were returned to their home cages.

Step-down inhibitory avoidance task

Latency in the step-down avoidance task was determined to evaluate the animals' performance, according to the previously described method (Kim et al. 2010b). Rats were trained in a step-down avoidance task 7 days after hypoxic ischemia induction. One hour after training, latency (sec) in each group was measured. In training sessions, the animals received a 0.5 mA scramble foot shock for 2 sec immediately upon stepping down. The time interval between the time at which the mouse stepped down and the time at which the mouce placed all four paws on the grid was defined as the latency time. Any latency period longer than 180 sec was recorded as 180 sec.

Radial eight-arm maze task

Spatial working memory was tested using a radial eight-arm maze apparatus consisting of a central octagonal plate (30 cm in diameter) and eight radiating arms (50 cm in length and 10 cm in width), according to the previously described method (Kim et al. 2010b). The test was conducted 10 days after induction of hypoxic ischemia and was terminated when a rat found the water in all eight arms or after more than 8 min had elapsed. Re-entering a previously visited arm was counted as an error. The number of correct choices before the first error was also recorded.

Tissue preparation

Brain tissues were prepared according to the previously described method (Kim et al. 2010c). Ten days after

starting the experiments, rats were sacrificed using Zoletil 50® (10 mg/kg, i.p.; Vibac Laboratories, Carros, France). A freezing microtome (Leica, Nussloch, Germany) was used to prepare 40-μm serial coronal sections, with an average of 10 slices each for the SN, striatum, and hippocampal dentate gyrus from each rat.

TH immunohistochemistry

Free-floating tissue sections were incubated overnight with mouse anti-TH antibody (1:1000; Santa Cruz Biotechnology, Santa Cruz, CA, USA), and sections were incubated for 1 h with biotinylated anti-mouse secondary antibody (1:200; Vector Laboratories, Burlingame, CA, USA).

BrdU immunohistochemistry

Sections were permeabilized via incubation in 0.5% Triton X-100 in PBS for 20 min, then pretreated in 50% formamide-2 × standard saline citrate (SSC) at 65°C for 2 h, denatured in 2 N HCl at 37°C for 30 min, and rinsed twice in 100 mM sodium borate (pH 8.5). Sections were incubated overnight at 4°C with BrdU-specific mouse monoclonal antibody (1:600; Roche). Sections were washed three times with PBS, incubated for 1 h with a biotinylated mouse secondary antibody (1:200; Vector Laboratories), and incubated for 1 h with avidin-peroxidase complex (1:100; Vector Laboratories). Sections were visualized via incubation in 50 mM Tris-HCl (pH 7.6) containing 0.03% DAB, 40 mg/ml nickel chloride, and 0.03% hydrogen peroxide for 5 min.

Data analysis

The areas of the SN and striatum from each slice were measured using an Image-Pro Plus computer-assisted image analysis system (Media Cyberbetics Inc., Silver Spring, MD, USA) attached to a light microscope (Olympus, Tokyo, Japan). The numbers of TH-positive cells in the SN were counted hemilaterally using a light microscope (Olympus). The TH-immunoreactive fiber density was measured in 100 μm × 100 μm square images of the striatum using an image analyzer. To estimate TH-staining density, optical densities were corrected for nonspecific background measured in completely denervated striatum areas. TH-positive fiber density ratios in the striatum were calculated as optical density in the lesion side divided by the optical density in the intact side.

The number of BrdU-positive cells in the dentate gyrus was counted, and the area of the granular layer of the dentate gyrus was measured using the Image-Pro Plus computer-assisted image analysis system (Media Cyberbetics Inc.). The number of BrdU-positive cells in the granular layer of the dentate gyrus was counted hemilaterally using a light microscope (Olympus). BrdU-positive data were expressed as the number of cells per square millimeter of granular area in the dentate gyrus.

Statistical analysis was performed using one-way ANOVA, followed by Duncan's post-hoc test, and results are expressed as the mean ± standard error of the mean (SEM). Significance was set as $P < 0.05$.

Results

Effect of hypothermia on the short-term memory in the step-down avoidance task

The latencies of the step-down avoidance task are presented in Figure 1. The animals' performance in a step-down inhibitory avoidance task was disturbed by induction of hypoxic ischemia injury ($P < 0.05$), and hypothermia treatment alleviated hypoxic ischemia-induced impairment of the animals' performance ($P < 0.05$). In contrast, hyperthermia exerted no significant effect on the animal's performance in the hypoxic ischemia-induced rats.

Effect of hypothermia on the spatial-learning memory in the radial eight-arm maze task

Data on successful performance time and the number of correct choices and errors in the radial eight-arm maze task are presented in Figure 2. These results indicated that induction of hypoxic ischemia resulted in

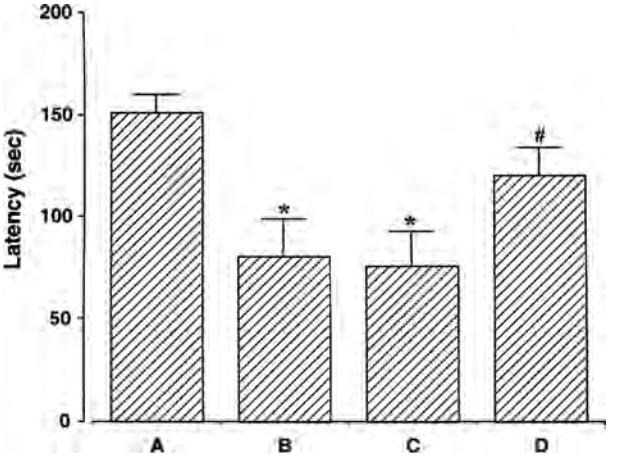

Figure 1. Effect of hypothermia treatment on the latency in a step-down avoidance task. (A) Sham-operation group, (B) hypoxic ischemia group, (C) hypoxic ischemia and hyperthermia group, (D) hypoxic ischemia and hypothermia group. *Represents $P < 0.05$ compared with the sham-operation group. #Represents $P < 0.05$ compared with the hypoxic ischemia group.

an increase in time for water seeking, a lower number of correct choices before the first error, and a higher number of errors ($P < 0.05$). Hypothermia treatment reduced the time seeking water, increased the number of correct choices, and decreased the error number ($P < 0.05$), demonstrating that hypothermia ameliorated the hypoxic ischemia-induced spatial-learning memory impairment. In contrast, hyperthermia exerted no significant effect on the spatial-learning memory in the hypoxic ischemia-induced rats.

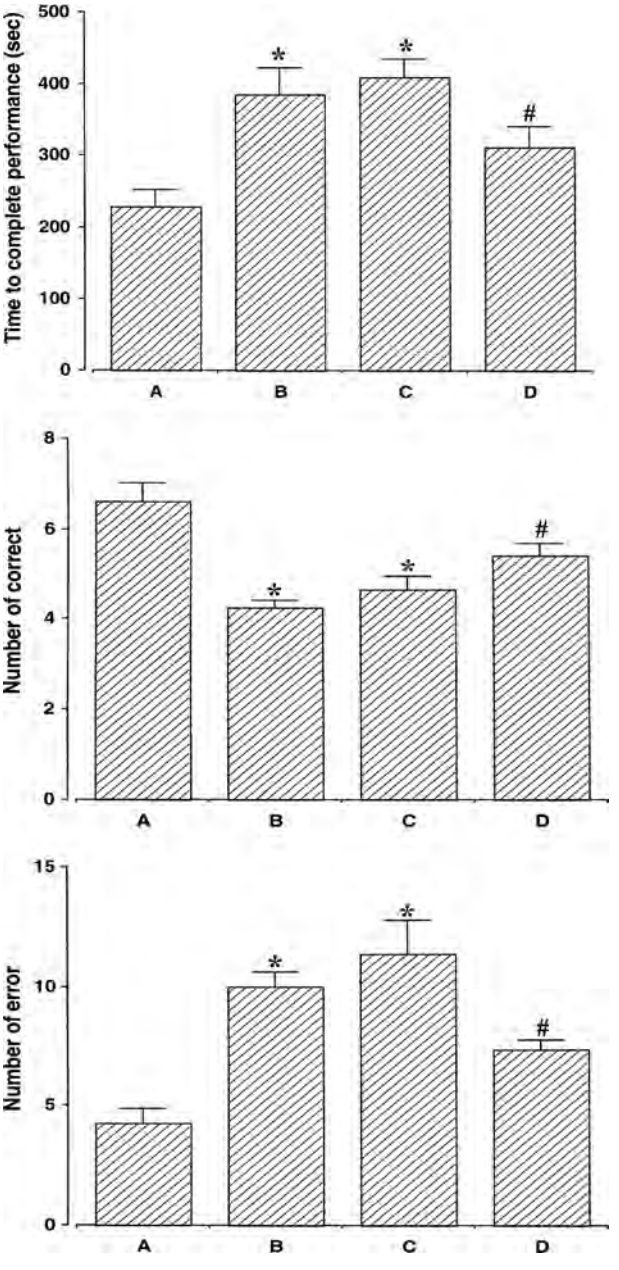

Figure 2. Effects of hypothermia treatment on time, correct performance, and errors in the radial eight-arm maze task. (A) Sham-operation group, (B) hypoxic ischemia group, (C) hypoxic ischemia and hyperthermia group, (D) hypoxic ischemia and hypothermia group. *Represents $P < 0.05$ compared with the sham-operation group. #Represents $P < 0.05$ compared with the hypoxic ischemia group.

Effect of hypothermia on TH-positive cells in the SN

Photomicrographs of TH-positive cells in the SN are presented in Figure 3. These results showed that hypoxic ischemia injury suppressed TH expression in the SN ($P < 0.05$), and hypothermia treatment significantly alleviated the hypoxic ischemia-induced decrease of TH expression in the SN ($P < 0.05$). In contrast, hyperthermia exerted no significant effect on the TH expression in the hypoxic ischemia-induced rats.

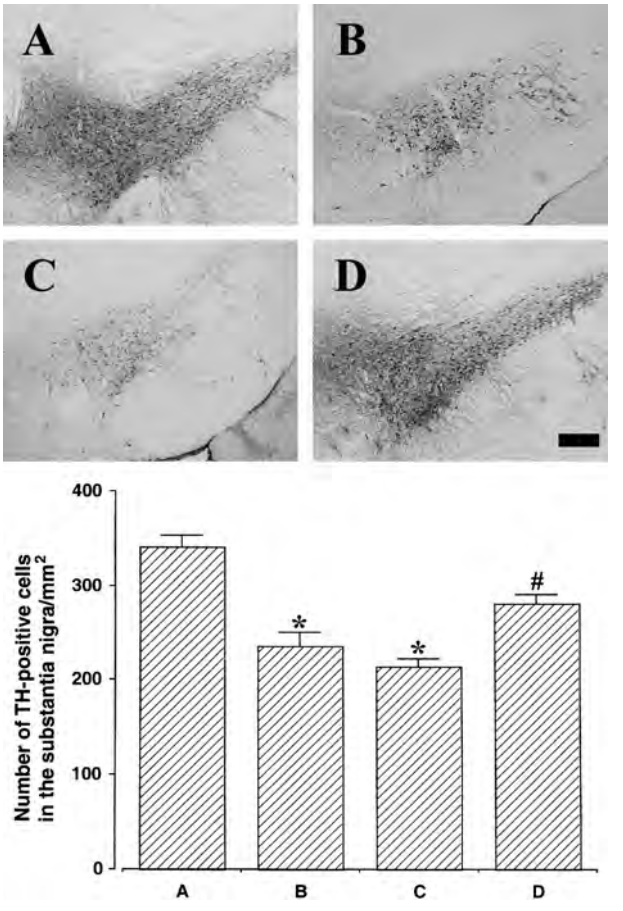

Figure 3. Effect of hypothermia treatment on tyrosine hydroxylase expression in the substantia nigra. Upper panel: photomicrographs of tyrosine hydroxylase (TH) expression in the substantia nigra (SN). (A) Sham-operation group, (B) hypoxic ischemia group, (C) hypoxic ischemia and hyperthermia group, (D) hypoxic ischemia and hypothermia group. Staining for TH immunoreactivity (brown). The scale bar represents 200 μm. Lower panel: TH expression in the SN. *Represents $P < 0.05$ compared with the sham-operation group. #Represents $P < 0.05$ compared with the hypoxic ischemia group.

Effect of hypothermia on TH expression in the striatum

Photomicrographs of TH-immunoreactive fibers in the striatum are presented in Figure 4. These results showed that hypoxic ischemia injury suppressed TH-immunoreactive fibers in the striatum ($P<0.05$), and hypothermia treatment significantly alleviated the hypoxic ischemia-induced decrease of TH-immunoreactive fibers in the striatum ($P<0.05$). In contrast, hyperthermia exerted no significant effect on the TH expression in the hypoxic ischemia-induced rats.

Effect of hypothermia on BrdU-positive cells in the dentate gyrus

Photomicrographs of BrdU-positive cells in the dentate gyrus are presented in Figure 5. These results showed that induction of hypoxic ischemia enhanced cell proliferation in the dentate gyrus ($P<0.05$), which is probably a compensatory adaptive response to hypoxic ischemia brain injury. Hypothermia treatment suppressed hypoxic ischemia-induced cell proliferation in the dentate gyrus ($P<0.05$). In contrast, hyperthermia

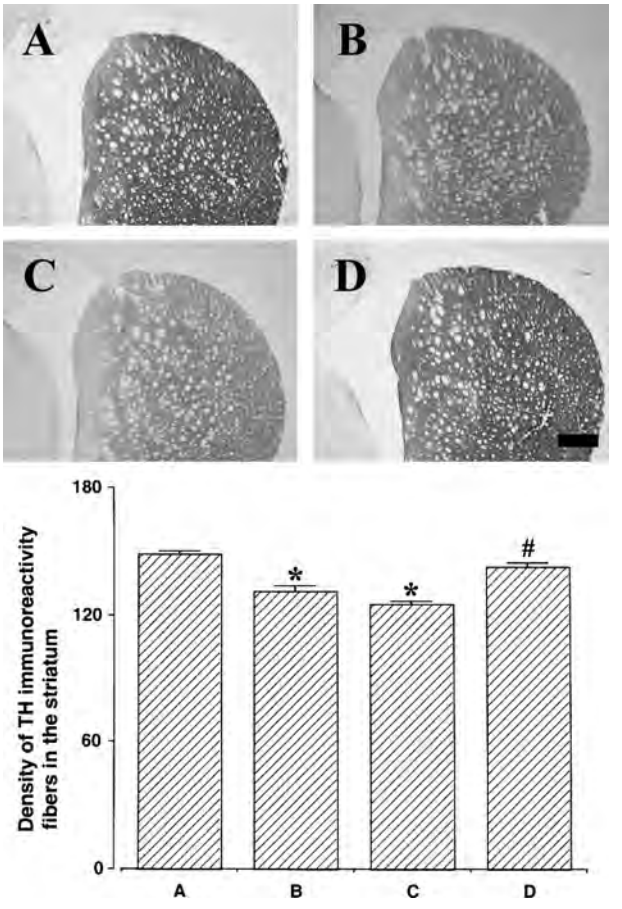

Figure 4. Effect of hypothermia treatment on tyrosine hydroxylase expression in the striatum. Upper panel: photomicrographs of tyrosine hydroxylase (TH) expression in the striatum. (A) sham-operation group, (B) hypoxic ischemia group, (C) hypoxic ischemia and hyperthermia group, (D) hypoxic ischemia and hypothermia group. Sections were stained for TH immunoreactivity (brown). The scale bar represents 200 μm. Lower panel: TH expression in the striatum. *Represents $P<0.05$ compared with the sham-operation group. #Represents $P<0.05$ compared with the hypoxic ischemia group.

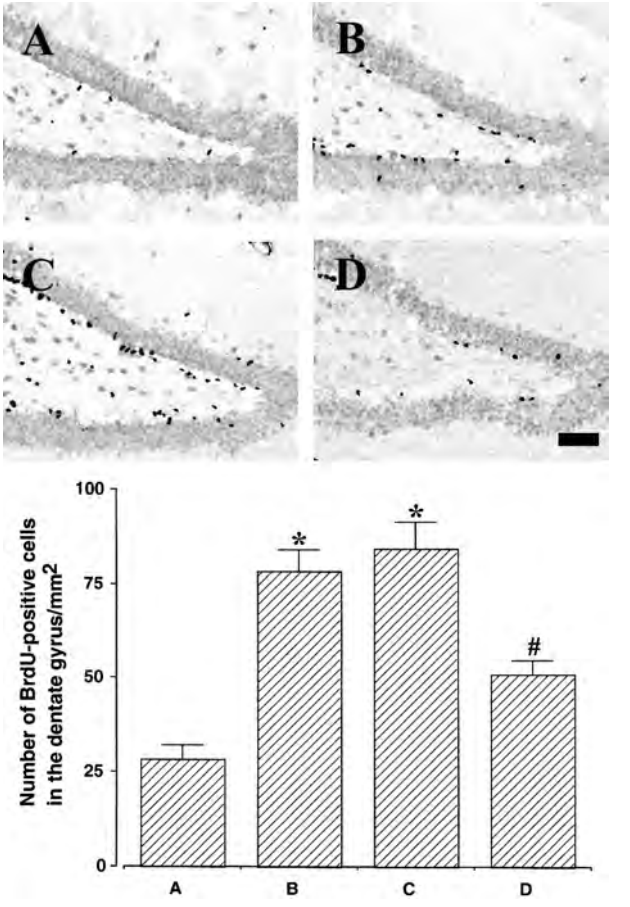

Figure 5. Effect of hypothermia treatment on cell proliferation in the dentate gyrus. Upper panel: photomicrographs of 5-bromo-2′-deoxyuridine (BrdU)-positive cells in the dentate gyrus. (A) Sham-operation group, (B) hypoxic ischemia group, (C) hypoxic ischemia and hyperthermia group, (D) hypoxic ischemia and hypothermia group. Sections were stained for BrdU (black) and neuronal nuclei (NeuN; brown). The scale bar represents 400 μm. Lower panel: number of BrdU-positive cells in the dentate gyrus. *Represents $P<0.05$ compared with the sham-operation group. #Represents $P<0.05$ compared with the hypoxic ischemia group.

exerted no significant effect on the cell proliferation in the hypoxic ischemia-induced rats.

Discussion

The brain is more sensitive organ to hypoxia than other organs, due to its high oxygen demand. Hypoxic episodes in the striatum, such as those encountered in ischemia or anoxia, deplete the ATP content, leading to neuronal loss through a massive release of neurotransmitters, mainly dopamine and glutamate (Banasiak et al. 2000; Orset et al. 2005). Midbrain dopamine neurons are well known for their strong responses to rewards and their critical role in positive motivation. Dopamine's contribution appears to be chiefly to cause wanting for hedonic rewards, more than liking or learning about those rewards (Berridge 2007). Dopamine appears necessary for normal wanting, and dopamine activation can be sufficient to enhance cue-triggered incentive salience. Dopamine has distinct roles in motivational control. Some dopamine neurons encode motivational value, supporting brain networks for seeking, evaluation, and value learning. Others encode motivational salience, supporting brain networks for orienting, cognition, and general motivation (Bromberg-Martin et al. 2010). Previous studies using in vivo brain microdialysis showed that hypoxic ischemia decreases the extracellular dopamine concentration in the striatum of freely moving adult rats (Parrot et al. 2003). TH activity is progressively decreased following the loss of dopamine neurons in the striatum as well as in the SN in the hypoxic-ischemia rodent model (Jakowec et al. 2004). Brain damage decreases TH expression in the SN and striatum (Park and Enikolopov 2010). In this study, significantly decreased TH expression in the striatum and SN was observed in the rats of the hypoxic-ischemia group compared with those in the sham-operation group. This indicates that hypoxic ischemia decreases TH expression in the striatum and SN.

New neurons are produced from neuronal stem and progenitor cells after a series of division, elimination, differentiation, and maturation events. Each step of this neurogenesis cascade can be affected by a variety of intrinsic and extrinsic factors, including neurotransmitters such as dopamine (Lledo et al. 2006; Zhao et al. 2008). Moreover, the neurogenic regions of the adult brain are innervated by dopaminergic projections from the SN and striatum. Therefore, a reduction of dopamine levels caused by brain injuries may affect the production of new neurons in the dentate gyrus. We found that cell proliferation in the hippocampal dentate gyrus was significantly increased following hypoxic ischemia, indicating that hypoxic ischemia induces cell proliferation in the hippocampal dentate gyrus. Hypoxic ischemia-induced enhancement of cell proliferation in the dentate gyrus has been suggested as a compensatory adaptive response to excessive apoptosis following ischemic brain injury (Liu et al. 1998; Ko et al. 2009) through alteration of dopaminergic inputs from the SN neurons (Borta and Höglinger 2007).

The neuroprotective effect of hypothermia can be attributed to a decrease in cerebral metabolic rate, diminished brain energy demands, and reduction in the rate of high-energy phosphate depletion, which subsequently promote post-ischemic metabolic recovery. Previous studies demonstrated that reduction of brain temperature by only 2–3°C prevents neuronal damage in highly vulnerable brain regions such as the hippocampus and striatum (Kvrivishwili 2002). Hachimi-Idrissi et al. (2004) reported that hypothermia significantly attenuates extracellular glutamate and dopamine overflow during reperfusion and substantially reduces cell proliferation after asphyxial cardiac arrest in rats. Our study showed that hypothermia treatment significantly ameliorated the hypoxic ischemia-induced decrease in TH expression in the SN and striatum. Furthermore, hypothermia treatment suppressed the hypoxic ischemia-induced increase of cell proliferation in the dentate gyrus.

Brain injuries, especially of the hippocampus, cause impairment of performance. Perinatal hypoxia leads to impaired performance as regards long-term spatial learning and memory. Dopamine receptor (D1/D5R) activation alleviates perinatal hypoxia-induced impaired performance (Chen et al. 2007). Ischemic injury in gerbils impaired memory and increased apoptotic neuronal cell death in the hippocampal CA1 region (Ko et al. 2009). Cortical impact injury in rats caused long-lasting working memory impairment (Kobori and Dash 2006). Traumatic brain injury (TBI) also increased latency in the step-down avoidance task with increasing apoptosis in the hippocampus, showing that injury to the hippocampus induced impairment of performance (Kim et al. 2010a). Bales et al. (2011) suggested that a TBI-induced neurological deficit is associated with a decrease in dopamine and cAMP regulated phosphoprotein 32 (DARPP-32) phosphorylation. Hypoxic ischemic brain injury is known to lead to mental retardation and deficits in cognitive abilities, such as learning and memory. Impairment of the performance of hypoxic ischemic rats in a water maze task was unlikely to be due to changes in motivation, sensorimotor function, or visual impairment (Kumral et al. 2004). A previous study suggested that impairment of performance in hypoxic ischemia rats was due to learning and memory deficits (Anderson and Arciniegas 2010). Deficits in learning and memory following hypoxic ischemia are closely correlated with dopamine dysfunction in the

nigrostriatal pathway and excessive cell proliferation in the hippocampus (Fan et al. 2006; Park and Enikolopov 2010).

Dopamine availability in both striatal and extrastriatal brain regions is known to be implicated in cognitive performance. Acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioning in mice caused associative memory impairments with depletion of dopamine throughout the brain (Vucković et al. 2008). Dopaminergic therapies after TBI illustrate the importance of dopamine for cognitive function/dysfunction after TBI (Bales et al. 2009). Our behavioral tests clearly indicated that hypoxic ischemia induces incapacitation of animals' performance and spatial working memory, which were significantly improved by hypothermia treatment.

This study suggests that hypothermia alleviates the animals' performance and spatial working memory deficits probably by preventing hypoxic ischemia-induced dopamine dysfunction. Hyperthermia treatment, in contrast, exerted no significant effects on memory, TH expression, or cell proliferation in rats with hypoxic ischemia injury. Here in this study, we propose that hypothermia treatment might overcome hypoxic ischemia-induced impairment of memory function through suppressing the decrement in dopamine synthesis, thus facilitating functional recovery following hypoxic ischemia injury to the brain.

Acknowledgements

This research was supported by the grant of 2008 Hanseo University, Korea (08-0320).

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