Dexmedetomidine Inhibits Hippocampal Neuronal Damage Caused by Persistent Isoflurane-Induced Hypotension in Rat Model of Chronic Cerebral Hypoperfusion

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Abstract

Purpose

The purpose of this study was to investigate the effect of dexmedetomidine (DEX) on hypotension-induced neuronal damage in a chronic cerebral hypoperfusion (CCH) model of rats, an established model of cerebral white matter lesions (WML) in humans, which is prevalent in the elderly and closely related to cognitive decline.

Methods

The CCH model rats were randomly assigned to one of four groups: normotension + no DEX (NN) group (n = 6), normotension + DEX (ND) group (n = 6), hypotension + no DEX (HN) group (n = 6), or hypotension + DEX (HD) group (n = 6). Under isoflurane anesthesia, mean arterial blood pressure was maintained at or above 80 mmHg (normotension) or below 60 mmHg (hypotension) for a duration of two hours. The DEX groups received 50 μg of DEX intraperitoneally. Two weeks later, the Y-maze test and, after preparing brain slices, immunohistochemical staining were performed using antibodies against neuronal nuclei (NeuN), microtubule-associated protein 2 (MAP2), glial fibrillary acidic protein (GFAP), and Ionized calcium-binding adapter molecule 1 (Iba1).

Results

Behavioral observations showed no significant differences among the groups. Significant reductions of both NeuN-positive cells and the MAP2-positive area were found in the hippocampal CA1 in the HN group compared with NN and ND groups, but not in the HD group. GFAP and Iba-1-positive areas were significantly increased in the HN group, but not in the HD group.

Conclusion

DEX significantly ameliorated hypotension-induced neuronal damage and both astroglial and microglial activation in the CA1 region of CCH rats.

Categories: Neurology, Anesthesiology
Keywords: dexmedetomidine, chronic cerebral hypoperfusion, hippocampal neuronal damage, cerebral white matter lesion, hypotension

Introduction

Cerebral white matter lesions (WMLs) are produced by chronic cerebral hypoperfusion (CCH), in the absence of cerebral infarction, which typically occurs when cerebral blood flow (CBF) is reduced to < 20% of normal levels, and in which neuronal cell bodies are mainly damaged [1-4]. The cerebral white matter is composed of myelinated axons and glia, especially oligodendrocytes that form the myelin sheath, whereas the cerebral gray matter is mainly composed of neuronal cell bodies (perikaryon), dendrites, and astroglial cells [4]. WML develops with age, particularly in patients with arterial hypertension, diabetes mellitus (DM), or cardiovascular diseases, is found in 27%-87% of > 65-year-old brains and has been demonstrated to be closely correlated with cognitive decline [1-4]. It has been demonstrated that patients with WML have a marked risk of postoperative cognitive dysfunction (POCD) [5], and the purpose of this study was to investigate whether WML is a major cause of POCD [6].

A rat model of CCH is characterized by WML and cognitive impairment and has been well-established as a model for patients with WML [4,7,8]. In this model, CBF decreases to 40%-82% of normal levels over a

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prolonged period without cerebral infarctions. CCH per se induces marked microglial activation and axonal damage in some brain regions, such as the caudoputamen, optic tract, corpus callosum, and cerebral cortex, without causing neuronal damage, i.e., cerebral infarction [4,7,8]. There is abundant evidence to suggest that oxidative stress and inflammatory responses play pivotal roles in WML [8,9]. We previously demonstrated that hypocapnia or hypotension, which leads to a further reduction of CBF, caused neuronal damage in the caudoputamen or hippocampus of rats with CCH [10,11], and ketamine, an N-methyl-D aspartate (NMDA) receptor antagonist and anti-inflammatory agent [12], ameliorated this neuronal damage [13]. Dexmedetomidine (DEX), a specific α2 adrenaline receptor agonist and an anti-inflammatory agent [14,15], is often used for sedation during mechanical ventilation in anesthesia and intensive care and has been reported to exhibit neuroprotective effects in not only animals with various insults to the brain but also humans [16,17]. In the present study, we investigated whether DEX could ameliorate neuronal damage induced by hypotension in CCH rats.

Materials And Methods

The study received approval from the animal research committee of Kindai University Faculty of Medicine (KAME-2022-075). Table *1* shows the overview of the groups, including their descriptions and the number of rats in each group. Twenty-four adult male Sprague-Dawley (SD) rats, aged 12 weeks and weighing between 380 and 450 g, were randomly allocated to one of four groups: normotension + no DEX (NN) group (n = 6, 25%), normotension + DEX (ND) group (n = 6, 25%), hypotension + no DEX (HN) group (n = 6, 25%), or hypotension + DEX (HD) group (n = 6, 25%).

Group	Description	Number of Tats
NN	normotension + no DEX	6
ND	normotension + DEX	6
HN	hypotension + no DEX	6
HD	hypotension + DEX	6

TABLE 1: Overview of the groups, their descriptions, and the number of rats in each group.

Preparation of CCH rats

Rats were anesthetized with 4% isoflurane and 50% O_2 and allowed to respire spontaneously. Before making the skin incision, 0.3 mL of 0.5% lidocaine was administered percutaneously. Bilateral common carotid arteries were then ligated using silk suture material [7,8,10,11]. Sham-operated rats underwent the same surgical procedure but without carotid artery ligation. Following the procedure, rats were maintained under controlled environmental conditions (ambient temperature: 23-26 °C, 12/12-hour light/dark cycle with lights on at 7 AM), with ad libitum access to food and water.

Induction of hypotension

Two weeks following the establishment of the CCH model, rats were anesthetized with isoflurane, intubated with the assistance of 0.1 mg/kg of vecuronium, and mechanically ventilated as follows: initial anesthesia induction was achieved with 4% isoflurane and 100% O_2 administered via a mask. Subsequently, anesthesia maintenance involved 3% isoflurane and 50% O_2, while mechanical ventilation was initiated. A tail vein cannulation was performed for drug administration, and the right femoral artery was cannulated to facilitate arterial blood pressure measurement and blood gas analysis sampling.

In the NN and ND groups, mean arterial pressure (MAP) was maintained at or above 80 mmHg (normotension) through phenylephrine injections if required. For the HN and HD groups, experimental conditions mirrored those of the NN and ND groups, but MAP was sustained below 60 mmHg (hypotension) by adjusting the isoflurane concentration. In the ND and HD groups, 50 μg (0.5 mL) of DEX was administered intraperitoneally, while an equal volume of normal saline was administered to the NN and HN groups immediately after mechanical ventilation setup.

Temporalis muscle temperature was monitored and maintained between 36.5 and 37.5°C using a warm water mattress and heating lamp. After maintaining MAP within the target range for two hours, anesthesia was discontinued, and tracheal extubation was performed. Rats were then maintained under the aforementioned conditions for an additional 14 days.

Behavioral test

The behavioral test was performed 14 days after rats were exposed to hypo- or normotension by isoflurane. Rats underwent a spontaneous alternation test to measure working memory in the Y-maze (Figure *1*). They were divided into three 120-degree-angle arms (30 cm high, 50 cm long, and 15 cm wide) labeled A, B, and C. The equilateral triangle formed by the three arms was 15 cm long. Arms were randomly set up as the start arm, the novel arm, and the other arm. Each rat was placed in the start arm. A video camera mounted on the top of the Y-maze recorded their movements for 8 min (Figure *2*), and the percentage of alternations (entries into arms different from the previous two entries) as spatial memory was calculated using the following formula (Alternations/Arm Entries - 2) x 100. After the behavioral test of each rat, the Y-maze was cleaned to remove odors and residues so that they would not affect the test results. During the behavioral test, the investigator was not visible to the rats. Sham-operated rats were set up for behavioral tests only.
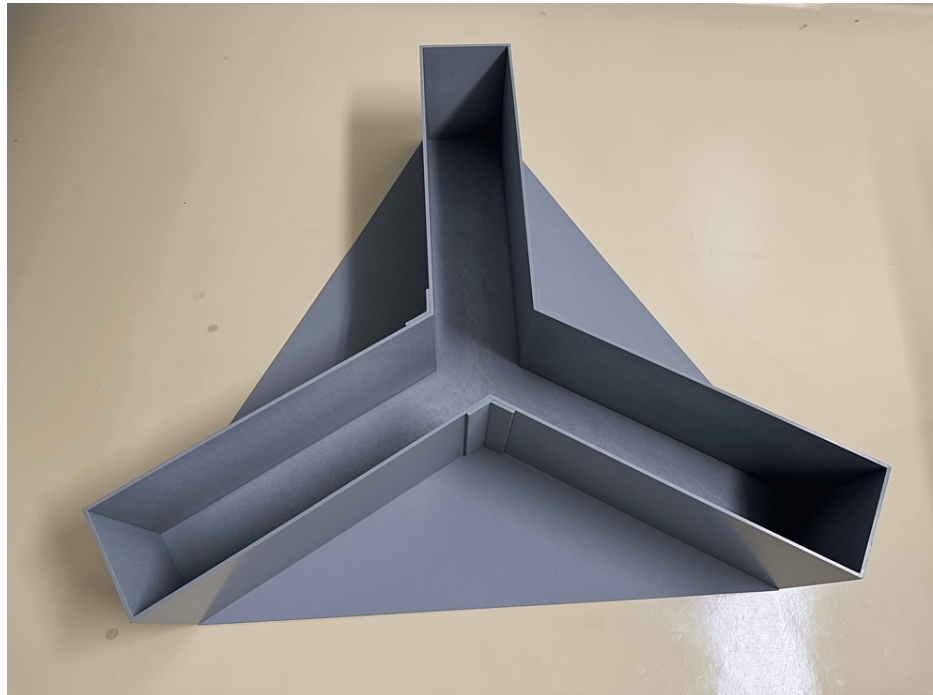
FIGURE 1: Y-maze

FIGURE 2: A video camera mounted on the top of the Y-maze

Preparation of brain slices and histopathology

Fourteen days following the completion of the behavioral test, rats were deeply anesthetized with isoflurane and transcardially perfused with 0.001 mol/L phosphate-buffered saline, followed by a fixative solution composed of 4% paraformaldehyde and 0.2% picric acid in 0.1 mol/L phosphate buffer (pH 7.4). The brain was then extracted, post-fixed in 4% paraformaldehyde in 0.1 mol/L phosphate buffer (pH 7.4) for 24 hours, and subsequently stored in 20% sucrose solution in 0.1 mol/L phosphate buffer (pH 7.4).

Brain tissue sections were obtained using a cryostat (thickness: 20 μm), and these sections were utilized for histological, immunohistochemical, or immunofluorescent analyses. Unless otherwise specified, all incubation procedures were conducted at room temperature.

Brain sections were treated with 3% H_2O_2 in Tris-buffered saline (TBS: 0.1 M Tris-HCl, pH 7.5, 0.15 M NaCl) containing 0.1% TritonX-100 (TBS-T) for 30 minutes. The sections were then washed three times with TBS-T, and incubated overnight at room temperature with mouse monoclonal antibodies against neuronal nuclei (NeuN) (Millipore, Billerica, MA, USA), as a neuronal marker that recognizes nuclear proteins, microtubule-associated protein-2 (MAP-2) (Sigma Aldrich, Burlington, MA, USA), which is located almost exclusively in the neuronal perikaryal and dendrites and the reduction of which indicates neuronal damage, and ionized calcium-binding adaptor molecule 1 (Iba1) (Wako Pure Chemical, Osaka, Japan), as a marker of microglia, or rabbit polyclonal antibody against glial fibrillary acidic protein (GFAP) (DAKO, Glostrup, Denmark), as a marker of astrocytes. After thorough washing, the sections were further incubated with HISTIFINE Rat-PO (multi)-kit (Nichirei, Osaka, Japan) consisting of a mixture of peroxidase-conjugated anti-mouse and rabbit IgG as a secondary antibody for 60 min at room temperature. The HISTIFINE Rat-PO kit contains pre-absorbed rat serum, and nonspecific binding by rat serum in damaged rat tissue was negligible. The label was visualized for 5 min using diaminobenzidine (DAB; Vector Peroxidase Substrate Kit; Vector Laboratories, Burlingame, CA, USA) and contrast-stained with hematoxylin, except for sections incubated with NeuN antibody. Hematoxylin-contrast staining was performed on all sections except for those incubated with NeuN antibody.

Morphometry and statistical analyses

Neuronal damage was quantified by counting the number of morphologically normal cell nuclei stained with NeuN in a given 0.04-mm^2 area of the hippocampal CA1 region in each hemisphere. Normal cell bodies and dendrites were calculated using image-processing software (Olympus BX53, Tokyo, Japan) for MAP2-positive areas in a given 0.04-mm^2 area of the hippocampal CA1 region in each hemisphere. Based on previous experiments [11], the hypothesis of this study was that there was a 30% difference between HN and HD groups in the development of neuronal damage. To detect this difference with a power of 80% and a P-value of 0.05, power calculations indicated that a sample size of at least six animals per group was required. Sample sizes were calculated using the G*power 3.1 statistical power analysis program (Heinrich-Heine-

University, Düsseldorf, Germany). Statistical comparisons of physiological variables between groups were performed using one-way analysis of variance (ANOVA) followed by the Bonferroni post-hoc test, and histological data between groups were analyzed using Kruskal-Wallis statistics followed by Dunn's post-hoc test. Results are expressed as mean ± standard deviation (SD) or median (IQR: interquartile range). p-values < 0.05 were considered significant. The power of statistical comparison was assessed using JMP14.2 Statistical Discovery Software (SAS Inst., Inc., Cary, NC).

Results

Table *2* shows the physiological parameters observed during mechanical ventilation. MAP exhibited a significant decrease in the HN and HD groups compared to the NN and ND groups. Heart rate, pH, PaO_2, $PaCO_2$, temperature, and blood glucose levels were all within normal physiological ranges and showed no significant differences across the groups.

|	NN group	ND group	HN group	HD group
Mean arterial pressure (mmHg)	108 ± 10	112 ± 7	55 ± 4*	56 ± 3*
Heart rate (bpm)	220 ± 40	238 ± 38	253 ± 34	241 ± 23
pH	7.422 ± 0.09	7.403 ± 0.07	7.392 ± 0.11	7.42 ± 0.03
$PaCO_2$ (mmHg)	42.2 ± 4.6	40.5 ± 3.8	39.4 ± 4.4	43.1 ± 3.1
PaO_2 (mmHg)	180.6 ± 49.3	201.3 ± 60.1	199.2 ± 52.5	210.4 ± 33.7
Temperature (°C)	37.0 ± 0.2	37.1 ± 0.2	37.1± 0.1	37.1 ± 0.1
Glucose (mg/dL)	150 ± 37	139 ± 28	150 ± 41	130 ± 23

TABLE 2: Physiological variables during anesthesia.

Values are mean ± SD (standard deviation)

NN group: normotension + no DEX group, ND group: normotension + DEX group, HN group: hypotension + no DEX group, HD group: hypotension + DEX group

*P < 0.05 vs. NN and ND groups

Behavioral testing showed no significant differences among the groups (Figure *3*). Figure *4a* shows a representative photomicrograph of immunostaining of both NeuN and MAP2 in the hippocampal CA1 region. CCH per se did not reduce normal cell counts (Figures *4a*, *4b*; NN and ND groups), but they were significantly decreased in the HN group, and DEX pretreatment significantly ameliorated the reduction (HD group). The HN group showed a significant reduction in the MAP2-positive area of the hippocampal CA1 region, but DEX pretreatment protected against this reduction (Figures *4a*, *4b*). Both microglia and astroglia (Figures *5a*, *5b*) were significantly activated in the HN group, but DEX significantly suppressed those activations. The morphological change of microglia from ameboid to ramified form was noted in the HN group.
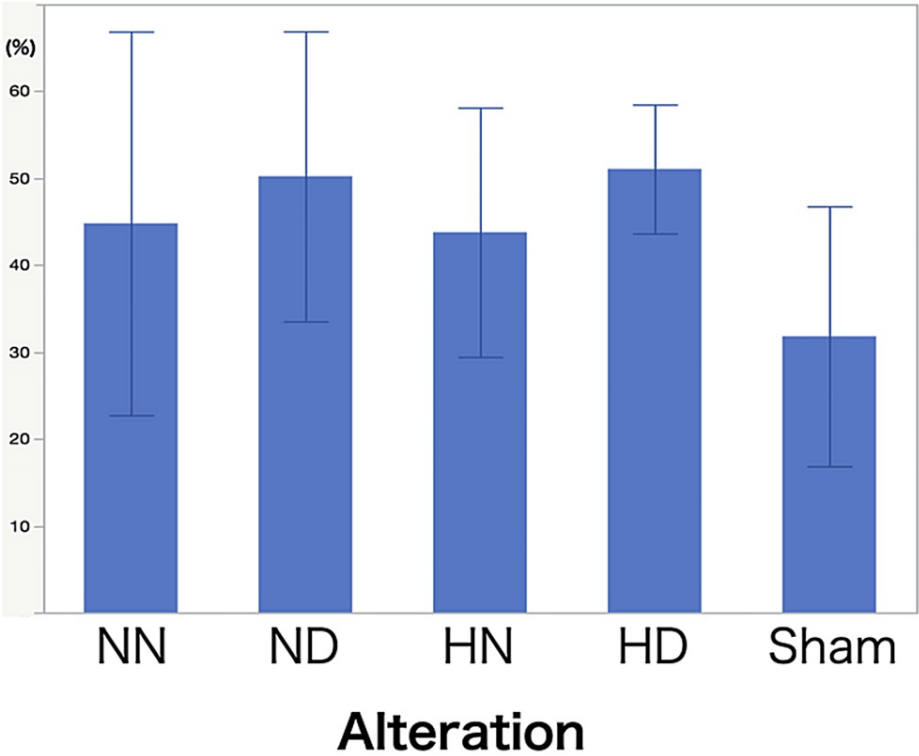
FIGURE 3: Behavioral test.

Results of a spontaneous alternation test to measure working memory in the Y-maze 14 days after rats were exposed to isoflurane-induced hypotension or normotension. In the behavioral testing, evaluation was conducted using alteration scores (%). The results are shown as mean and standard deviation. There were no significant differences in the alteration scores among the four groups of rats: NN (normotension + no dexmedetomidine) group, ND (normotension + dexmedetomidine) group, HN (hypotension + no dexmedetomidine) group, and HD (hypotension + dexmedetomidine) group. Behavioral testing showed no significant differences among the groups.

Values are mean ± SD (standard deviation)

*$P < 0.05$ vs. NN and ND groups
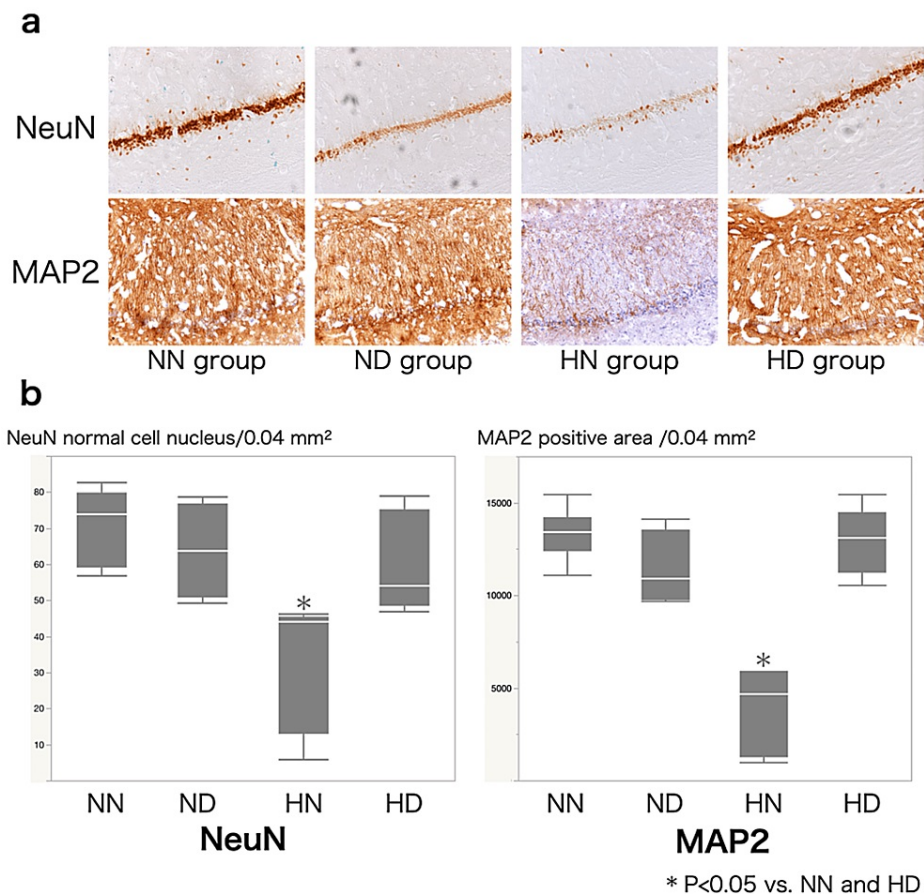
FIGURE 4: Photomicrograph of both NeuN and MAP2 in the hippocampal CA1 region.

(a) Photomicrograph of both NeuN and MAP2 in the hippocampal CA1 region in the NN (normotension + no dexmedetomidine) group, ND (normotension + dexmedetomidine) group, HN (hypotension + no dexmedetomidine) group, and HD (hypotension + dexmedetomidine) group. (b) Box and whisker plots depicting the counts of normal neuronal cells in predefined areas (0.04 mm2) within the hippocampal CA1 region across the NN, ND, HN, and HD groups. The values are presented as the median (represented by the transverse line inside the boxes), interquartile range (IQR) denoted by the boxes, and the 10th–90th percentiles illustrated by the whiskers. NN and ND groups did not show a reduction in normal cell counts, but they were significantly decreased in the HN group. The HN group showed a significant reduction in the MAP2-positive area of the hippocampal CA1 region, but dexmedetomidine pretreatment protected against the reduction.

*P < 0.05 vs. NN and HD groups
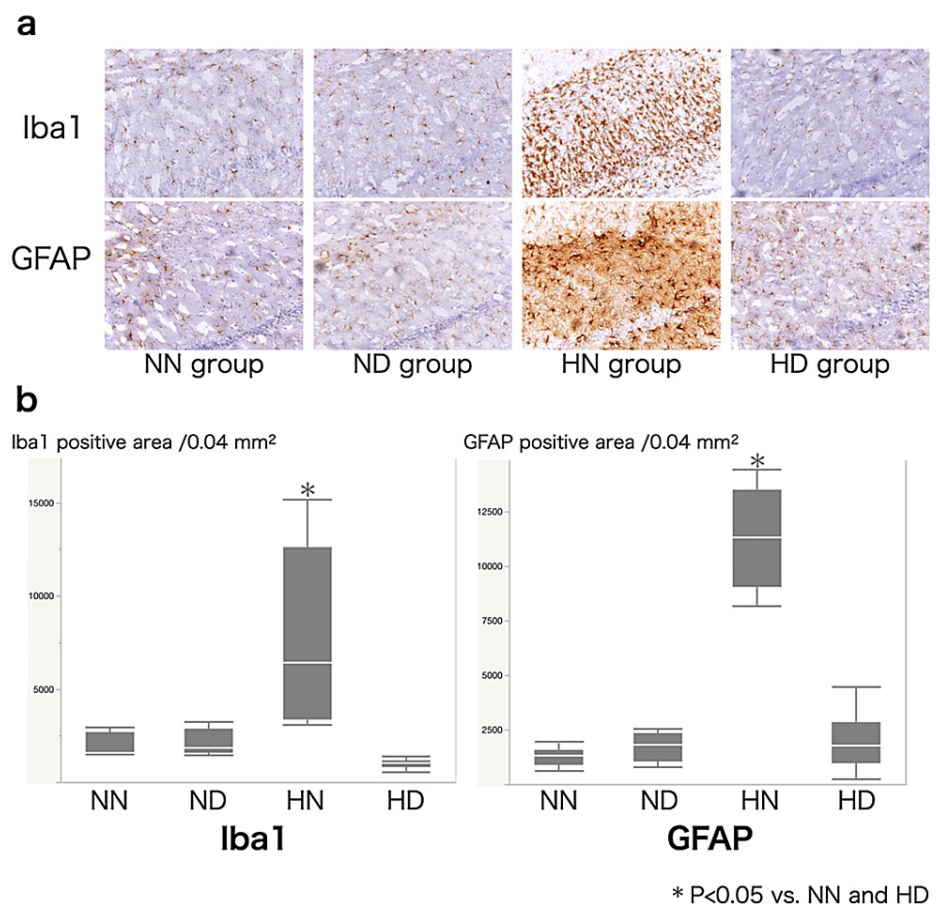
FIGURE 5: Photomicrograph of both Iba1 and GFAP in the hippocampal CA1 region.

a Photomicrographs of both Iba1 and GFAP immunohistochemical staining of the hippocampal CA1 region in the NN (normotension + dexmedetomidine non-administration) group, ND (normotension + dexmedetomidine) group, HN (hypotensive + dexmedetomidine non-administration) group, and HD (hypotensive + dexmedetomidine) group.

b Box and whisker plots of Iba1 and GFAP-positive regions in predetermined areas (0.04 mm2) of the hippocampal CA1 region in NN, ND, HN, and HD groups. NN and ND groups did not show an increase in the positive area, but it was significantly increased in the HN group.

Values are expressed as median (transverse line inside boxes), IQR (boxes), and 10–90 percentiles (whiskers).

*P < 0.05 vs. NN and HD groups

Discussion

We demonstrated that CCH per se induced WML but not CA1 neuronal damage in rats, and exposure of CCH rats to persistent hypotension resulted in activation of both microglia and astrocytes and CA1 neuronal damage, being consistent with previous studies [7,8,10,11]. Curiously, the results of the behavioral test (Y maze test) did not differ among groups, even with the massive CA1 neuronal damage group (HN group). DEX significantly suppressed the glial activation and neuronal damage in CA1.

WML is caused by CCH without apparent neuronal damage, i.e., cerebral infarction, and is closely associated with cognitive decline [9,10,12-14]. A rat model of CCH has been used as a well-established model of global WML and vascular dementia in humans [9,10,12-14]. We previously demonstrated that hypocapnia [10] or hypotension [11], both of which can reduce CBF, caused massive CA1 neuronal damage as well as marked microglial and astroglial activation in CCH rats, but those insults per se could not cause the neuronal damage in normal rats. In the present study, we confirmed that CCH per se did not induce pyramidal neuronal cell damage in CA1; persistent hypotension caused the neuronal damage (Figures *2a*, *2b*), probably because CBF in CA1 of CCH rats was reduced to less than 20% of normal blood flow.

The definition of hypotension in rats is not clear, but as normal mean blood pressure under general anesthesia is around 90 mmHg [10,18] and the mean blood pressure drops to 40 mmHg during hemorrhagic

shock in SD rats, we defined normotension as ⩾ 80 mmHg and moderate hypotension as ⩽ 60 mmHg [18].

NeuN protein is localized in nuclei and perinuclear cytoplasm of most neurons in the central nervous system of mammals and used as a neuromarker [19], and MAP2, which stabilizes microtubules, is located almost exclusively in perikaryal regions and dendrites. Therefore, a decrease in the count of NeuN staining or the area of MAP2 staining indicates neuronal damage [10]. Microglia are immune cells that are resident in the brain and activated in response to ischemia and other insults, secreting various factors such as cytokines, chemokines, and oxygen radicals, and activated microglia induce neuronal damage [10]. In this study, not only an increase in the number of microglia but also a morphological change of microglia from ameboid to ramified form was noted in the HN group, indicating that further reduction in the CBF by persistent hypotension caused the glial activation, which was significantly suppressed by DEX in the HD group (Figures 3a, 3b). Astrocytes are heterogeneous and have diverse functions that can contribute to tissue repair and promote CNS pathology in the context of trauma, infection, and neurodegenerative diseases [20]. Astrocytes are activated by inflammation and also contribute to the progression of inflammation.

CA1 of the hippocampus is highly vulnerable to global cerebral ischemia not only in animals but also in humans [21,22], and the damage of CA1 pyramidal cells causes cognitive damage, especially special learning impairment, which can be detected by Morris water maze testing in rodents [21,23,24]. In the present study, however, rats whose CA1 neurons were markedly damaged did not show memory impairment on Y maze testing. The discrepancy may be due to the sensitivity of the Y maze test and/or the results of some reports which showed that the intensity of CA1 neuronal damage did not necessarily correlate with the severity of behavioral impairment [21,23,24].

DEX is a specific α2 adrenaline receptor agonist and has been demonstrated to exhibit anti-inflammatory activity in animals [14] and humans [14,15], and consequently provide cardio- [15] or neuro- [16,17] protection against various insults. In the present study, DEX significantly suppressed the activation of both microglia and astrocytes, probably through its anti-inflammatory effect, and exerted neuronal protection in CA1 in CCH rats exposed to persistent hypotension. Although DEX is usually used as a continuous infusion in clinical settings, in the present study, a single dose of 50 μg DEX was administered intraperitoneally to rats. However, it has been reported that a single administration of intraperitoneal DEX could induce prolonged DEX plasma elevation and exhibit various stable effects in rats: Kato et al. reported that the sedative effect was prolonged over 90 min after 30 or 100 μg/kg DEX intraperitoneal administration in rats [25]. Dawson and colleagues demonstrated that the antinociceptive effective dose 50 (ED50) of a single intraperitoneal administration of DEX in rats was 27.6 ± 5.1 μg/kg, and the antinociceptive effect persisted for up to 90 min [26]. Bol et al. reported that plasma DEX levels remained high even at 90 min after intraperitoneal administration of 30 μg/kg DEX to rats [27].

CCH rats feature WML without apparent neuronal damage, i.e., cerebral infarction. WML is prevalent in elderly people and patients with DM, hypertension, and cerebrovascular diseases [28-30]. In an intensive care unit, patients under mechanical ventilation are sometimes elderly have hypertension, DM, and/or cerebrovascular diseases, and are at risk of persistent hypotension [31-33]. As DEX is widely used for sedation in patients under mechanical ventilation, we believe that it is a good choice for sedation, especially in patients with WML from the perspective of neuroprotection.

Our study had several limitations. First, we did not measure the actual CBF of rats; thus, we did not know the exact reduction of CBF caused by hypotension. Second, we used isoflurane as a hypotension-inducing agent because we wanted to avoid using another drug to induce hypotension. General anesthetics, including isoflurane, theoretically have some neuroprotective effects on the brain [34,35], but in contrast, only isoflurane has been reported to have some harmful effects on the nervous system [36]. In the present study, however, as all groups were exposed to isoflurane, we believe that the effects of isoflurane could be disregarded.

Conclusions

In a rat model of CCH, persistent hypotension caused inflammation in the brain probably due to CBF reduction and consequently hippocampal CA1 neuronal damage, which all were suppressed by DEX. The results suggest that DEX is a good choice for sedation of patients under mechanical ventilation, especially elderly patients, and/or patients with hypertension, DM, and/or cerebrovascular diseases to prevent neuronal damage and/or cognitive decline.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Takashi Mino, Shinichi Nakao

Disclosures

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References

1. Desmond DW: Cognition and white matter lesions. Cerebrovasc Dis. 2002, 13 Suppl 2:53-7. 10.1159/000049151
2. Schmidt R, Scheltens P, Erkinjuntti T, et al.: White matter lesion progression: a surrogate endpoint for trials in cerebral small-vessel disease. Neurology. 2004, 63:139-44. 10.1212/01.wnl.0000132635.75819.e5
3. Pantoni L: Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010, 9:689-701. 10.1016/S1474-4422(10)70104-6
4. Nakao S, Xu Y: White matter injury in global cerebral ischemia. White Matter Injury in Stroke and CNS Disease. Carmichael S Jr, Baltan S (ed): Springer, New York, NY; 2014. 181-96. 10.1007/978-1-4614-9123-1
5. Maekawa K, Baba T, Otomo S, Morishita S, Tamura N: Low pre-existing gray matter volume in the medial temporal lobe and white matter lesions are associated with postoperative cognitive dysfunction after cardiac surgery. PLoS One. 2014, 9:e87375. 10.1371/journal.pone.0087375
6. Nakao S, Yamamoto T, Kimura S, Mino T, Iwamoto T: Brain white matter lesions and postoperative cognitive dysfunction: a review. J Anesth. 2019, 33:336-40. 10.1007/s00540-019-02613-9
7. Wakita H, Tomimoto H, Akiguchi I, Kimura J: Glial activation and white matter changes in the rat brain induced by chronic cerebral hypoperfusion: an immunohistochemical study. Acta Neuropathol. 1994, 87:484-92. 10.1007/BF00294175
8. Wakita H, Tomimoto H, Akiguchi I, Kimura J: Protective effect of cyclosporin A on white matter changes in the rat brain after chronic cerebral hypoperfusion. Stroke. 1995, 26:1415-22. 10.1161/01.str.26.8.1415
9. Dewar D, Underhill SM, Goldberg MP: Oligodendrocytes and ischemic brain injury. J Cereb Blood Flow Metab. 2003, 23:263-74. 10.1097/01.WCB.0000053472.41007.F9
10. Miyamoto E, Tomimoto H, Nakao Si S, Wakita H, Akiguchi I, Miyamoto K, Shingu K: Caudoputamen is damaged by hypocapnia during mechanical ventilation in a rat model of chronic cerebral hypoperfusion. Stroke. 2001, 32:2920-5. 10.1161/hs1201.100216
11. Yamamoto T, Iwamoto T, Kimura S, Nakao S: Persistent isoflurane-induced hypotension causes hippocampal neuronal damage in a rat model of chronic cerebral hypoperfusion. J Anesth. 2018, 32:182-8. 10.1007/s00540-018-2458-z
12. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y: Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. Anesth Analg. 2012, 115:934-43. 10.1213/ANE.0b013e3182662e30
13. Miyamoto E, Nakao S, Tomimoto H, et al.: Ketamine attenuates hypocapnia-induced neuronal damage in the caudoputamen in a rat model of chronic cerebral hypoperfusion. Neurosci Lett. 2004, 354:26-9. 10.1016/j.neulet.2003.09.058
14. Flanders CA, Rocke AS, Edwardson SA, Baillie JK, Walsh TS: The effect of dexmedetomidine and clonidine on the inflammatory response in critical illness: a systematic review of animal and human studies. Crit Care. 2019, 23:402. 10.1186/s13054-019-2690-4
15. Chen M, Li X, Mu G: Myocardial protective and anti-inflammatory effects of dexmedetomidine in patients undergoing cardiovascular surgery with cardiopulmonary bypass: a systematic review and meta-analysis. J Anesth. 2022, 36:5-16. 10.1007/s00540-021-02982-0
16. Jiang L, Hu M, Lu Y, Cao Y, Chang Y, Dai Z: The protective effects of dexmedetomidine on ischemic brain injury: a meta-analysis. J Clin Anesth. 2017, 40:25-32. 10.1016/j.jclinane.2017.04.003
17. Wang Y, Han R, Zuo Z: Dexmedetomidine-induced neuroprotection: is it translational?. Transl Perioper Pain Med. 2016, 1:15-9.
18. Wang Y, Cong Y, Li J, Li X, Li B, Qi S: Comparison of invasive blood pressure measurements from the caudal ventral artery and the femoral artery in male adult SD and Wistar rats. PLoS One. 2013, 8:e60625.

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10.1371/journal.pone.0060625

19. Gusel'nikova VV, Korzhevskiy DE: Neun as a neuronal nuclear antigen and neuron differentiation marker . Acta Naturae. 2015, 7:42-7.

20. Giovannoni F, Quintana FJ: The role of astrocytes in CNS inflammation . Trends Immunol. 2020, 41:805-19. 10.1016/j.it.2020.07.007

21. Nunn J, Hodges H: Cognitive deficits induced by global cerebral ischaemia: relationship to brain damage and reversal by transplants. Behav Brain Res. 1994, 65:1-31. 10.1016/0166-4328(94)90069-8

22. Petito CK, Feldmann E, Pulsinelli WA, Plum F: Delayed hippocampal damage in humans following cardiorespiratory arrest. Neurology. 1987, 37:1281-6. 10.1212/wnl.37.8.1281

23. Auer RN, Jensen ML, Whishaw IQ: Neurobehavioral deficit due to ischemic brain damage limited to half of the CA1 sector of the hippocampus. J Neurosci. 1989, 9:1641-7. 10.1523/JNEUROSCI.09-05-01641.1989

24. Olsen GM, Scheel-Krüger J, Møller A, Jensen LH: Relation of spatial learning of rats in the Morris water maze task to the number of viable CA1 neurons following four-vessel occlusion. Behav Neurosci. 1994, 108:681-90. 10.1037//0735-7044.108.4.681

25. Kato RI, Tachibana K, Hashimoto T, Takita K, Morimoto Y: Dexmedetomidine suppresses long-term potentiation in the hippocampal CA1 field of anesthetized rats. J Anesth. 2014, 28:828-32. 10.1007/s00540-014-1853-3

26. Dawson C, Ma D, Chow A, Maze M: Dexmedetomidine enhances analgesic action of nitrous oxide: mechanisms of action. Anesthesiology. 2004, 100:894-904. 10.1097/00000542-200404000-00020

27. Bol CJ, Vogelaar JP, Mandema JW: Anesthetic profile of dexmedetomidine identified by stimulus-response and continuous measurements in rats. J Pharmacol Exp Ther. 1999, 291:153-60.

28. Breteler MMB, van Amerongen NM, van Swieten JC, et al.: Cognitive correlates of ventricular enlargement and cerebral white matter lesions on magnetic resonance imaging: the Rotterdam Study. Stroke. 1994, 25:1109-15. 10.1161/01.str.25.6.1109

29. Erkinjuntti T, Gao F, Lee DH, Eliasziw M, Merskey H, Hachinski VC: Lack of difference in brain hyperintensities between patients with early Alzheimer's and control subjects. Arch Neurol. 1994, 51:260-8.

30. Lindgren A, Roijer A, Rudling O, et al.: Cerebral lesions on magnetic resonance imaging, heart disease, and vascular risk factors in subjects without stroke. A population-based study. Stroke. 1994, 25:929-34. 10.1161/01.str.25.5.929

31. Vincent JL, Nielsen ND, Shapiro NI, et al.: Mean arterial pressure and mortality in patients with distributive shock: a retrospective analysis of the MIMIC-III database. Ann Intensive Care. 2018, 8:107. 10.1186/s13613-018-0448-9

32. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ: Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012, 21:1151-60.

33. Green RS, Turgeon AF, McIntyre LA, et al.: Postintubation hypotension in intensive care unit patients: a multicenter cohort study. J Crit Care. 2015, 30:1055-60.

34. Xiong L, Zheng Y, Wu M, Hou L, Zhu Z, Zhang X, Lu Z: Preconditioning with isoflurane produces dose-dependent neuroprotection via activation of adenosine triphosphate-regulated potassium channels after focal cerebral ischemia in rats. Anesth Analg. 2003, 96:233-7, table of contents. 10.1097/00000539-200301000-00047

35. Kitano H, Kirsch JR, Hurn PD, Murphy SJ: Inhalational anesthetics as neuroprotectants or chemical preconditioning agents in ischemic brain. J Cereb Blood Flow Metab. 2007, 27:1108-28. 10.1038/sj.jcbfm.9600410

36. Schallner N, Ulbrich F, Engelstaedter H, Biermann J, Auwaerter V, Loop T, Goebel U: Isoflurane but not sevoflurane or desflurane aggravates injury to neurons in vitro and in vivo via p75NTR-NF-κB activation. Anesth Analg. 2014, 119:1429-41. 10.1213/ANE.0000000000000488

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