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Effects of delta-opioid agonist SNC80 on white matter injury following spinal cord ischemia in normothermic and mildly hypothermic rats

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Abstract
Purpose. Although the delta-opioid agonist SNC80 has been shown to attenuate hind-limb motor function and gray matter injury in normothermic rats subjected to spinal cord ischemia (SCI), its effects on white matter injury remain undetermined. In the present study, we investigated whether SNC80 could attenuate white matter injury in normothermic and mildly hypothermic rats.
Methods. Forty rats were randomly allocated to one of following five groups: vehicle or SNC80 with 10 min of SCI at 38°C (V-38-10m or SNC-38-10m, respectively), vehicle or SNC80 with 22 min of SCI at 35°C (V-35-22m or SNC-35-22m, respectively), or sham. SNC80 or vehicle was intrathecally administered 15 min before SCI. Forty-eight hours after reperfusion, the white matter injury was evaluated by the extent of vacuolation.
Results. The percent area of vacuolation in the ventral white matter was significantly lower in the SNC-38-10m and SNC-35-22m groups compared with that in the V-38-10m and V-35-22m groups, respectively ($P < 0.05$).
Conclusion. The results indicate that intrathecal treatment with the delta-opioid agonist SNC80 can attenuate the ventral white matter injury following SCI in rats under normothermic and mildly hypothermic conditions.

Key words Spinal cord ischemia · Delta-opioid agonist · White matter injury · Normothermia · Mild hypothermia

Introduction

As a consequence of thoracic and thoracoabdominal aortic aneurysm surgery, some patients develop paraparesis or paraplegia resulting from spinal cord ischemia (SCI). A number of investigators have conducted research on protecting the spinal cord against SCI, using hypothermia [1,2] or various pharmacological approaches [3]. The data from our previous study showed that the pre-ischemic intrathecal administration of a highly selective, nonpeptidic delta-opioid agonist, SNC80, (+)-4-[(αR)-α((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N, N-diethyl-benzamide, attenuated spinal cord injury after SCI in normothermic rats [4]. Because hypothermia has been consistently shown to protect the spinal cord subjected to SCI, the combined use of hypothermia and pharmacological agents might show a significant protective effect on the ischemic spinal cord.

Studies of central nervous system ischemia have mainly focused on gray matter injury. However, Kanellopoulos et al. [5] have indicated that there is severe white matter injury in the spinal cord after SCI, and that an alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate (AMPA)/kainite receptor antagonist reduced white matter injury and improved locomotor function. Their result suggests that the evaluation of white matter injury might be important after SCI. In the present study, we therefore investigated the effects of a delta-opioid agonist, SNC80, on white matter injury in rats, in addition to the effects on hind-limb motor function and gray matter injury following SCI, under normothermic (38°C) and mildly hypothermic (35°C) conditions.

Materials and methods

The Animal Experiment Committee of Nara Medical University (Nara, Japan) approved this study. Male Sprague-Dawley rats (Japan SLC, Shizuoka, Japan) weighting 350 to 450 g were used in this study.

Implantation of an intrathecal catheter was performed as previously reported [6], with some modification. In brief, 40 rats were anesthetized, in an acrylic box, with 5% isoflurane in an air/oxygen mixture. After induction, the anesthesia was maintained with 1.5% isoflurane via a snout cone. The animals' heads were mounted in a stereotaxic frame. Polyethylene tubing (PE-10) was

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inserted and advanced 8.5 cm caudal to the level of lumbar enlargement of the spinal cord via the atlantooccipital membrane. The rats were returned to their cages and housed for 4–7 days. SNC80 (Alexis Japan, Tokyo, Japan) was prepared in vehicle (20% dimethyl sulfoxide and 100 mM HCl) so that 10-µl contained 400 nmol of SNC80.

SCI was induced as reported by Taira and Marsala [7]. Briefly, rats that had been implanted with intrathecal catheters and showed no neurological deficits were anesthetized again in an acrylic box with 5% isoflurane in an air/oxygen mixture. After induction, the tracheas were intubated and the lungs were ventilated mechanically with 1.5% isoflurane in an air/oxygen mixture. Rectal and paravertebral muscle temperatures were continuously monitored and controlled with a heat lamp and a water blanket. For monitoring distal arterial blood pressure and collecting blood specimens, a PE-50 catheter was inserted into the tail artery. A 2F Fogarty balloon catheter was inserted via the left femoral artery to the descending thoracic aorta so that the tip of the catheter reached the level of the left subclavian artery (10.8 to 11.4 cm from the site of insertion). A PE-60 catheter was inserted into the left carotid artery and connected to an external blood reservoir positioned at 54 cm above the rat's body to reduce arterial blood pressure above the occlusion site during aortic occlusion, to a target of 40 mm Hg. Immediately after all cannulations, the rats received 200 U of heparin injected into the tail artery.

After the above preparation, the rats were randomly allocated to one of the following five groups (n = 8 each): vehicle or SNC80 with 10 min of SCI under normothermia (38°C; V-38-10m or SNC-38-10m, respectively), vehicle or SNC80 with 22 min of SCI under mild hypothermia (35°C; V-35-22m or SNC-35-22m, respectively), or sham. The 22-min duration of ischemia at 35°C was determined based on the data in our preliminary study, in which the degree of hind limb motor function after 22 min of SCI at 35°C was similar to that after 10 min of SCI at 38°C.

SNC80 or vehicle was given 15 min before the induction of SCI, followed by 20 µl of saline to flush the catheter. The investigator was blinded to the content of the syringes. Fifteen minutes after intrathecal administration, the Fogarty balloon catheter was inflated with 0.05 ml of saline to occlude the descending aorta. The efficiency of the occlusion was assessed by an immediate and sustained loss of any detectable pulsation and a decrease in pressure below the level of the aortic occlusion. After 10 or 22 min of SCI, the balloon was deflated, and blood was reinfused for 30 s. The catheters were then removed and incisions closed. Protamine sulfate (4 mg) was administered subcutaneously before the animals recovered from anesthesia. Blood gases, pH, and hematocrit were measured 10 min before and 10 min after SCI. In the V-35-22m and SNC-35-22m groups, the bodies of rats were gradually rewarmed, within 2 h after SCI, to 38°C. The rectal temperature was monitored for 3 h after reperfusion. In the sham group, all catheters were inserted in the same manner as in the other groups, but the balloon was not inflated.

An observer who was blinded to the experimental procedures carefully examined the hind-limb motor function of the rats 48 h after SCI. Hind-limb motor function was assessed using the scoring system of the Basso, Beattie, Bresnahan (BBB) locomotor rating scale [8]. In brief, the scale has 22 levels, which range from 0 (total paralysis) to 21 (normal locomotion). Scores in the range of 1 to 8 are given for small or large movements of the three hind-limb joints without plantar weight support or dorsal stepping. A score of 9 involves attainment of plantar weight support or dorsal stepping. Scores of 10 to 20 are given for progressive improvements in coordinated walking ability. The right hind-limb motor function was assessed in order to exclude any effects of catheter insertion into the left femoral artery.

Forty-eight hours after reperfusion, the rats were deeply anesthetized with 5% isoflurane. The rats were then transcardially perfused with 100 ml of heparinized saline, followed by 150 ml of 10% buffered formalin. Twenty-four hours after the perfusion, the spinal cords were removed and postfixed in the same fixative as postfixed with 10% buffered formalin for 1–2 days. After this period, L4 and L5 spinal segments were dissected, embedded in paraffin, and cut transversely to a thickness of 5 µm. For histological assessments, these specimens were stained with hematoxylin and eosin. Gray matter injury was evaluated on the basis of the number of normal neurons in the ventral horn. Cells that contained Nissl substance in the cytoplasm, loose chromatin, and prominent nucleoli were considered to be normal neurons. The number of normal neurons per 0.5 mm^2 of tissue in Rexed's laminae VII, VIII, and IX was counted in both sides of the spinal cord gray matter under high-power microscopic magnification (200×) in a blinded fashion. The total number of normal neurons in six microscopic fields with total areas of 3 mm^2 was obtained for each section at L4 and L5 and then averaged. White matter injury was assessed on the basis of the extent of vacuolation in the ventral white matter [9]. The percentages of areas of vacuolation of the total target area (0.04 mm^2) were calculated. The total area was divided into 144 subareas for ventral and ventrolateral white matter. Then the number of subareas in which vacuoles occupied more than 75% of the subarea was counted, and the percentage of the number of subareas was calculated as the percent area of vacuolation. The percent areas of vacuolation in L4 and L5 were averaged.

Differences in physiological variables, the number of normal neurons, and the percent areas of vacuolation among the groups were assessed using one-factor analysis of variance, followed by the Student-Newman-Keuls test for multiple comparisons; the data values were expressed as means ± SD. The BBB scale was analyzed using the Kruskall-Wallis test followed by the Mann-Whitney *U*-test; the data values were expressed as medians (25th–75th percentiles). A probability value of less than 0.05 was considered statistically significant.

Results

Physiological variables are shown in Table 1. Before ischemia, there were no significant differences in pH, Pa_{CO_2}, Pa_{O_2}, hematocrit, glucose, or mean arterial pressure (MAP) among the groups. During the ischemia, distal MAP values in the ischemic groups were significantly lower compared with that in the sham group ($P < 0.05$). Immediately after reperfusion, pH values were significantly lower in the ischemic groups compared with that in the sham group ($P < 0.05$), and glucose in the SNC-35-22m group was significantly lower compared with that in the sham group ($P < 0.05$). Rectal and paravertebral muscle temperatures in the V-35-22m and SNC-35-22m groups were kept around 35°C until reperfusion (Table 1). After reperfusion, only rectal temperature was monitored, and the animals were rewarmed within 2 h (Table 2). There were no significant differences in rectal and paravertebral muscle temperatures between the V-38-10m and SNC-38-10m groups or between the V-35-22m or SNC-35-22m groups.

The BBB scores in the experimental groups are shown in Table 3. The BBB score in the SNC-38-10m group was significantly higher compared with that in the V-38-10m group ($P < 0.05$), whereas there were no statistically significant differences in BBB scores between the SNC-35-22m and V-35-22m groups. The results for number of normal neurons are shown in Table 4. The number of normal neurons in the SNC-38-10m group was significantly higher compared with that in the V-38-10m group ($P < 0.05$), whereas there were no statistically significant differences in the number of normal neurons between the SNC-35-22m and V-35-22m groups.

In the ventral white matter (Fig. 1), the percent area of vacuolation was significantly higher in the V-38-10m and V-35-22m groups compared with those in the SNC-38-10m group and the SNC-35-22m groups, respectively ($P < 0.05$). Representative histological findings in the ventral white matter are shown in Fig. 2. Vacuolation was more prominent in the V-35-22m group (Fig. 2b)

Table 1. Physiologic variables

	Sham	V-38-10m	SNC-38-10m	V-35-22m	SNC-35-22m
Body weight (g)	388 ± 32	409 ± 41	394 ± 45	393 ± 39	389 ± 30
Before ischemia					
pH	7.41 ± 0.04	7.40 ± 0.04	7.40 ± 0.05	7.38 ± 0.04	7.39 ± 0.05
P_{CO_2} (mm Hg)	39 ± 4	40 ± 4	39 ± 3	39 ± 4	37 ± 4
Pa_{O_2} (mm Hg)	151 ± 26	149 ± 14	149 ± 36	160 ± 27	69 ± 26
Hematocrit (%)	42 ± 4	43 ± 2	41 ± 2	44 ± 3	42 ± 3
Glucose (g/dl)	121 ± 39	135 ± 45	114 ± 14	117 ± 36	129 ± 47
Distal MAP (mm Hg)	105 ± 17	94 ± 11	86 ± 11	99 ± 10	96 ± 15
Rectal temperature (°C)	37.9 ± 0.1	38.0 ± 0.1	38.1 ± 0.1	35.0 ± 0.1*	34.9 ± 0.1*
Paravertebral muscle temperature (°C)	38.0 ± 0.1	38.0 ± 0.1	38.0 ± 0.1	35.0 ± 0.1*	35.0 ± 0.1*
During ischemia					
Distal MAP (mm Hg)	106 ± 18	8 ± 3*	7 ± 2*	6 ± 1*	7 ± 1*
Rectal temperature (°C)	38.0 ± 0.2	38.0 ± 0.1	38.1 ± 0.1	35.0 ± 0.1*	34.9 ± 0.1*
Paravertebral muscle temperature (°C)	37.9 ± 0.1	38.0 ± 0.1	38.0 ± 0.1	35.0 ± 0.1*	35.0 ± 0.1*
Immediately after ischemia					
pH	7.404 ± 0.04	7.22 ± 0.03*	7.22 ± 0.03*	7.09 ± 0.04*	7.11 ± 0.03*
P_{CO_2} (mm Hg)	40 ± 3	42 ± 6	46 ± 7	47 ± 8	46 ± 6
Pa_{O_2} (mm Hg)	155 ± 20	185 ± 28	173 ± 30	190 ± 16	183 ± 51
Hematocrit (%)	45 ± 2	44 ± 4	45 ± 3	48 ± 4	47 ± 2
Glucose (g/dl)	137 ± 17	129 ± 54	103 ± 22	97 ± 49	79 ± 29*
Distal MAP (mm Hg)	105 ± 15	111 ± 16	99 ± 17	93 ± 21	103 ± 20
Rectal temperature (°C)	38.0 ± 0.1	38.0 ± 0.1	37.9 ± 0.1	35.0 ± 0.1*	35.0 ± 0.1*
Paravertebral muscle temperature (°C)	38.0 ± 0.1	38.0 ± 0.1	38.0 ± 0.1	35.0 ± 0.1*	34.9 ± 0.1*

* $P < 0.05$ vs sham

Data values are expressed as means ± SD

MAP, mean arterial pressure; V-38-10m and SNC-38-10m, animals received 10-min spinal cord ischemia (SCI) 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 38°C during SCI; V-35-22m and SNC-35-22m, animals received 22-min SCI 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 35°C during SCI

Table 2. Changes in rectal temperature after reperfusion

	Sham	V-38-10m	SNC-38-10m	V-35-22m	SNC-35-22m
Rectal temperature after reperfusion (°C)					
15 min after reperfusion	37.9 ± 0.1	38.0 ± 0.1	38.0 ± 0.1	36.6 ± 0.7*	36.8 ± 0.5*
1 h after reperfusion	38.0 ± 0.2	38.0 ± 0.2	38.0 ± 0.3	37.2 ± 0.5*	37.1 ± 0.7*
2 h after reperfusion	38.0 ± 0.1	38.0 ± 0.2	38.1 ± 0.2	38.0 ± 0.2	37.9 ± 0.2
3 h after reperfusion	38.0 ± 0.1	38.0 ± 0.2	38.0 ± 0.2	37.9 ± 0.2	37.8 ± 0.1

* $P < 0.05$ vs sham
Data values are expressed as means ± SD
V-38-10m and SNC-38-10m, animals received 10-min spinal cord ischemia (SCI) 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 38°C during SCI; V-35-22m and SNC-35-22m, animals received 22-min SCI 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 35°C during SCI

Table 3. Basso, Beattie, Bresnahan (BBB) Locomotor Rating Scale scores 48 h after reperfusion

Sham	V-38-10m	SNC-38-10m	V-35-22m	SNC-35-22m
21 (21–21)	3 (0–9)	10.5 (7.5–17.5)*	5.5 (0–14.5)	9.5 (6–16)

* $P < 0.05$ vs V-38-10m
Data values are expressed as medians (25–75 percentiles)
V-38-10m and SNC-38-10m, animals received 10-min spinal cord ischemia (SCI) 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 38°C during SCI; V-35-22m and SNC-35-22m, animals received 22-min SCI 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 35°C during SCI

Table 4. The number of normal neurons

Sham	V-38-10m	SNC-38-10m	V-35-22m	SNC-35-22m
174 ± 2	91 ± 64	154 ± 54*	115 ± 58	136 ± 25

* $P < 0.05$ vs V-38-10m
Data values are expressed as means ± SD
V-38-10m and SNC-38-10m, animals received 10-min spinal cord ischemia (SCI) 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 38°C during SCI; V-35-22m and SNC-35-22m, animals received 22-min SCI 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 35°C during SCI

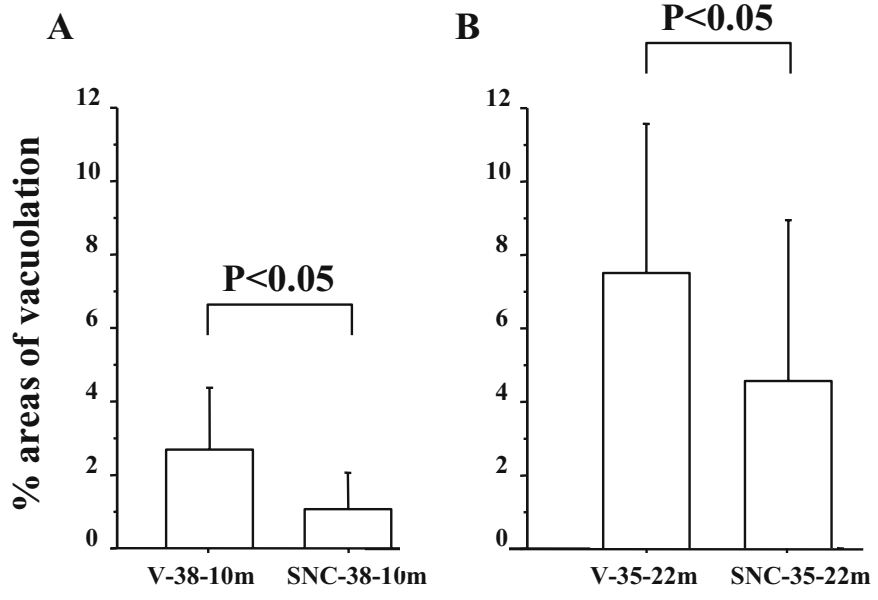

Fig. 1A,B. White matter injury was assessed on the basis of the extent of vacuolation in the ventral white matter in the normothermic (**A**) and mildly hypothermic (**B**) groups. The percentage of the area with vacuolations of the total target area (0.04 mm^2) in the ventral white matter was measured. Data values are expressed as means ± SD, *V-38-10m and SNC-38-10m*, animals received 10-min spinal cord ischemia (SCI) 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 38°C during SCI; *V-35-22m and SNC-35-22m*, animals received 22-min SCI 15 min after intrathecal treatment with vehicle (20% dimethyl sulfoxide) or SNC80, respectively, with rectal temperature 35°C during SCI

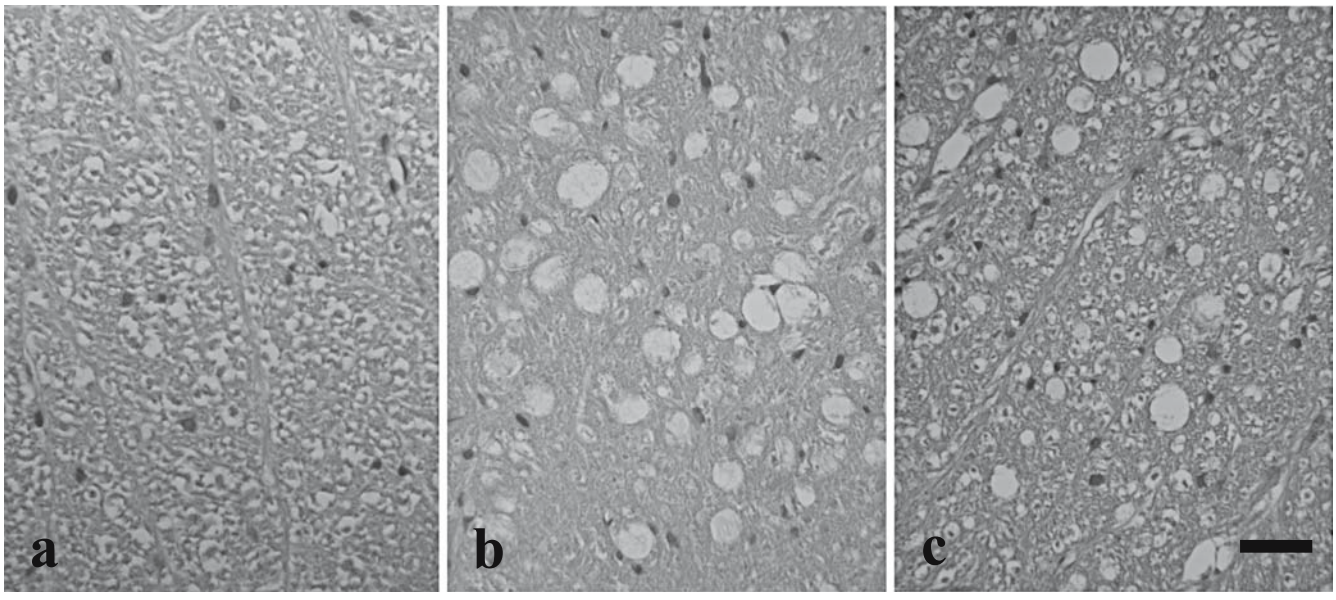

Fig. 2a–c. Representative histological findings of hematoxylin- and eosin-stained sections in the ventral white matter in the sham (**a**) and hypothermic groups (**b, c**). Vacuolation was not noted in the sham group (**a**). Vacuolation was more prominent in the V-35-22m group (**b**) compared with that in the SNC-35-22m group (**c**). *Scale bar*, 50 μm

compared with that in the SNC-35-22m group (Fig. 2c).

Discussion

For the assessment of spinal cord injury following SCI, gray matter injury has been mainly focused on as a target for therapy, because of the traditional view that white matter is less vulnerable to ischemic injury than gray matter. However, recent evidence has suggested the importance of white matter injury as well as gray matter injury following SCI. Follis et al. [10] demonstrated that white matter was more vulnerable to ischemia than gray matter in a rat model of SCI. Kanellopoulos et al. [5] indicated that the assessment of gray matter only may not be sufficient as an indicator of spinal cord injury, and that therefore it would be better to assess both gray matter and white matter. Vacuolations have been used as an indicator of white matter damage in the brain and spinal cord. Pantoni et al. [11] demonstrated that vacuolation and pallor of the white matter were very marked 24 h after ischemia and reflected the segmental swelling of myelinated axons, the formation of spaces between myelin sheaths and axolemma, and astrocyte swelling. Our previous study also showed that SCI induced vacuolations in the ventral and ventolateral areas of white matter in rats, and that amyloid precursor protein immunoreactivity, which is a marker of axonal damage, was accumulated in the regions of swollen axons in the ventral and ventrolateral white matter [9]. In the present study, we evaluated white matter injury as well as gray matter injury, and found that the delta-opioid agonist SNC80 attenuated the injury in the ventral white matter under both normothermic and mildly hypothermic conditions.

Delta-opioid receptor agonism prolonged cell survival in various organs in animal models, including the lung, heart, liver, and kidney [12]. In the central nervous system, Zhang et al. [13] found that delta-, but not mu- and kappa-, opioid receptor activation protected neocortical neurons from glutamate-induced excitotoxic injury. Tsao et al. [14] reported that delta-opioid receptor activation reduced methamphetamine-induced neuronal damage in the striatum. Data from our laboratory also showed that intrathecal treatment with the delta-opioid agonist SNC80 attenuated the hind-limb motor function and gray matter injury in normothermic rats subjected to SCI [4]. These findings are consistent with the results obtained in the present study under normothermic conditions.

The results in the present study indicated that, under mild hypothermia, SNC80 attenuated white matter injury in the ventral white matter, whereas it had no neuroprotective efficacy on hind-limb motor function or gray matter injury. The reasons that SNC80 had different influences on the gray and white matter injury under mild hypothermia are unknown. We suggest the following possible explanation. First, in our preliminary study, we determined the spinal cord ischemic duration at 35°C as 22 min, based on data in which the degree of hind limb motor function after 22 min of SCI at 35°C

was similar to that after 10 min of SCI at 38°C. However, the degree of white matter injury tended to be more severe after 22 min of SCI at 35°C than that after 10 min of SCI at 38°C. These findings suggested that the effects of hypothermia on gray and white matter injury after SCI might be different. Second, the mechanisms of cell death in gray and white matter have been shown to be different [15]. Therefore, the influence of SNC80 might have different effects on gray and white matter injury after SCI. Further study will be required to clarify these points.

The cellular and molecular mechanisms underlying the neuroprotection given by delta-opioid agonists against white matter injury after transient SCI are unknown. Because delta-opioid receptors are coupled to G proteins, G protein activity, along with the downstream signaling pathway, may be involved in the initial steps of delta-opioid receptor-mediated neuroprotection [13]. In addition, several reports indicating the neuroprotective properties of delta-opioid agonists suggest that extracellular signal-regulated protein kinase [16], protein kinase C [17], and voltage-dependent calcium channels may be involved [18]. However, further study is required to clarify the mechanism of SNC80-mediated white matter protection.

We note several limitations of the present study. First, in this study, we determined the doses of SNC80 based on the data of previous studies [19] and our pilot work. The results in our pilot work showed that 400 nmol of SNC80 had maximal efficacy for neuroprotection under normothermia (38°C). However, under mild hypothermia, the effective dose of SNC80 might be different from that under normothermia. Second, in the present study, neurological and histological assessments were performed 48 h after reperfusion. To reach definitive conclusions on the neuroprotective efficacy of SNC80 under normothermic and hypothermic conditions, long-term assessments will be required.

In summary, we investigated the effects of intrathecal treatment with the delta-opioid agonist SNC80 on white matter injury, in addition to hind-limb motor function and gray matter injury, under normothermic and mildly hypothermic conditions in rats subjected to SCI. The results indicate that this intrathecal delta-opioid agonist can attenuate the white matter injury following SCI in rats under both normothermic and mildly hypothermic conditions. These findings suggest that intrathecal SNC80 may be one possible candidate as a pharmacological adjunct for preventing white matter injury after SCI under both normothermic and mildly hypothermic conditions.

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