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ARTICLE

The beneficial aspects of spasticity in relation to ambulatory ability in mice with spinal cord injury

Shingo Yoshizaki[1,2] · Kazuya Yokota[1] · Kensuke Kubota[3] · Takeyuki Saito[1] · Masatake Tanaka[2] · Dai-jiro Konno[2] · Takeshi Maeda[3] · Yoshihiro Matsumoto[1] · Yasuharu Nakashima[1] · Seiji Okada[2]

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Abstract

Study design Experimental study with mice.

Objectives Spasticity is a common complication after spinal cord injury (SCI) and has detrimental aspects, such as persistent pain and involuntary muscle spasms. This study aimed to assess the influence of antispastic therapy on locomotor function after SCI.

Setting University-based laboratory in Fukuoka, Japan.

Methods A mouse model of spasticity was developed by producing incomplete SCI at the 9th thoracic level. At 8 weeks after SCI, an antispastic drug, baclofen, was intraperitoneally administered to six injured and two sham-operated mice. The severity of spasticity was evaluated by the modified Ashworth scoring (MAS) system, and locomotor function was evaluated by the Basso–Beattie–Bresnahan (BBB) scale/Basso mouse score (BMS).

Results The administration of baclofen significantly improved spasticity in the SCI mice and the mean MAS decreased to from 6.2 to 2.8. However, at the same time, it significantly exacerbated the locomotor dysfunction of the SCI mice and the mean BMS decreased from 4.7 to 2.3. The time-course of the changes in locomotor function coincided with the time-course of the spasticity score. We also confirmed that the administration of baclofen was not associated with any changes in either locomotor function or spasticity of the sham-operated control mice.

Conclusions Our results suggest that spasticity has a certain beneficial effect on ambulation ability. It is important to note that antispastic treatments may be associated with a risk of impairing the preserved function of chronic SCI patients.

Introduction

Spasticity is a common disabling condition associated with chronic spinal cord injury (SCI). For more than 100 years, spasticity has been defined as "disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles" [1]. This definition includes velocity-dependent increase in tonic stretch reflexes (muscle tone) and phasic stretch reflexes (exaggerated tendon jerks) [2]. Such aberrant somatic reflexes can interfere with mobility, transfer, self-care, social participation, caregiving, sleep, the sexual function, and activities of daily living (ADLs) [3]. If left untreated, spastic patients often develop involuntary muscle spasm and disabling contracture in the soft tissue [4–6]. Thus, effective relief from spasticity is expected to bring great benefits to chronic SCI patients.

The mechanisms of spinal spasticity include the loss of descending tracts' integrity and a decrease in gamma aminobutyric acid (GABA)/glycine-ergic presynaptic inhibition in segments caudal to the lesions [7]. For the clinical management of spasticity, various options to eliminate the triggers of the spinal hyperreflexia have been suggested, such as antispastic medications, focal injections of botulinum toxin, and invasive surgical operations [8]. Baclofen is an antispastic drug that is available worldwide. Since baclofen is a selective GABA-B receptor agonist, this drug

✉ Seiji Okada
seokada@ortho.med.kyushu-u.ac.jp

1 Department of Orthopedic Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

2 Department of Immunology and Neuroscience, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan

3 Department of Orthopaedic Surgery, Japan Labor Health and Welfare Organization, Spinal Injuries Center, Fukuoka, Japan

reduces the influx of calcium and suppresses the release of excitatory neurotransmitters, such as glutamate and aspartate. However, due to the existence of the blood spinal cord barrier, orally administered baclofen has very low bioavailability to the GABAergic neurons in the spinal cord [8], and is often limited by side effects or dose ceilings [9]. On the other hand, when baclofen is intrathecally administered, an efficient concentration within the cerebrospinal fluid can be achieved with a relatively smaller dose [10]. Thus far, many clinical reports have demonstrated that the intrathecal delivery of baclofen by an infusion pump significantly improved ADLs in chronic SCI patients by reducing spasticity-related pain and muscle rigidity [11]. However, we experienced some difficult cases in which chronic SCI patients were unexpectedly hindered from utilizing their preserved function with baclofen. Indeed, the functional aspects of spasticity and the association between the degree of spasticity and ambulatory disability remain elusive.

The aim of this study was to objectively assess the contribution of spasticity to functional activities in ambulant spastic SCI patients. Firstly, we established a mouse model of spasticity with contusive thoracic SCI and evaluated the time-course of the changes in lower-limb spasticity and locomotor function after the intraperitoneal administration of baclofen. In addition, we report a representative case of chronic SCI patient who exhibited significant changes in both spasticity and ambulation ability after the intrathecal administration of baclofen. Summarizing the above, baclofen treatment improved spasticity but was associated with a risk of impairing the preserved ambulatory function, thus suggesting the beneficial aspects of spasticity in relation to the ambulatory ability of SCI patients.

Methods

Mice

Adult 8-to-10-week-old female C57BL/6N mice (Japan SLC, Japan) were used in this study. All mice were housed in a temperature- and humidity-controlled environment on a 12-h light–dark cycle. All surgical procedures and experimental manipulations were approved by the Committee of Ethics on Animal Experimentation in the Faculty of Medicine, our institution (A28-251-0). Experiments were conducted under the control of the Guidelines for Animal Experimentation. All efforts were made to reduce the number of animals used and to minimize their suffering. We certify that all applicable institutional and governmental regulations concerning the ethical use of animals were followed during the course of this research.

Spinal cord injury and the administration of baclofen

To produce a mouse model of spasticity, six mice were anesthetized with an intraperitoneal injection of mixed anesthesia using medetomidine hydrochloride (0.3 mg/kg), midazolam (4 mg/kg), and butorphanol tartrate (5 mg/kg). After laminectomy at the 9th thoracic (T9) level, the dorsal surface of dura matter was exposed. The vertebral column was stabilized with fine forceps and clamps at the T8 and T10 spinous processes and ligament, and then the animal's body was lifted. SCI was induced by a moderate (70 kdyn) contusion injury using an Infinite Horizon Impactor (Precision Systems Instrumentation, Lexington, KY, USA), as previously described [12]. Immediately after injury, the overlying muscles were sutured, and the skin was closed with wound clips. During recovery from anesthesia, the mice were placed in a temperature-controlled chamber until thermoregulation was reestablished. Two sham-operated control mice were subjected to laminectomy alone at the T9 level. Baclofen (0.3 μg; Gabalon® 0.05%; Daiichi Sankyo Co, Ltd, Japan) was intraperitoneally administered to both the spastic mice and the control mice.

Assessment of the severity of spasticity

In both mice and humans, the modified Ashworth score (MAS) was determined for the lower limbs. After passive movement of the lower limbs, the sum of the scores of right and left sides was calculated. Our modified 0–5 scale was used for the qualitative rating of reaction to fast manual movement (Table 1). Only one stretch was used at each

Table 1 Definition of the MAS.

Score	Definition
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release of by minimal resistance at the end of the range of motion (ROM) when the affected part(s) is moved in flexion of extension
2	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
3	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
4	Considerable increase in muscle tone, passive movement difficult
5	Affected part(s) rigid in flexion or extension

speed. Every test was performed in a double-blind manner, as previously described [13, 14].

Assessment of the locomotor function

In mice, the motor function of the hindlimbs was evaluated by the locomotor rating test on the Basso–Beattie–Bresnahan (BBB) scale and the Basso mouse score (BMS) [15, 16]. A team of two experienced examiners evaluated each animal for 4 min and assigned an operationally defined score for each hindlimb. All measurements were taken on each side for three consecutive steps and averaged. Every test was performed in a double-blind manner, as previously described [12]. In addition, to show the time-course change of ambulation ability in both mice and humans objectively, representative images photographed with a video camera are shown in Figs. 2b and 3a, b.

Statistical analyses

Statistical analyses were performed with Wilcoxon's rank-sum test and Dunnett's test. For multiple comparisons between groups, a one-way ANOVA with a post hoc Tukey–Kramer test was used. P values < 0.05 were considered to indicate statistical significance. The data in graphs are presented as mean ± SD. All statistical analyses were performed using the JMP software program (version12; SAS Institute, Cary, NC, USA).

Results

The intraperitoneal administration of baclofen improved spasticity in mice with chronic SCI

To examine the functional characteristics of spasticity in this study, we first established a mouse model of spinal spasticity. At 8 weeks after SCI, all six injured mice exhibited hindlimb spasticity of substantial severity of spasticity, whereas sham-operated mice did not exhibit any spasticity (Fig. 1a).

Next, to confirm the antispastic effect of baclofen, we compared the severity of spasticity before and after the intraperitoneal administration of baclofen. At 2 hours post administration (h), the MAS was significantly reduced from a preadministration score of 6.2 (1.1) to a postadministration score of 2.8 (1.6) (mean [SD], Fig. 1a). Regarding the time-course of the change of MAS, at 1 h it was decreased in comparison with that at 0 h, and bottomed at 2 h. Thereafter, the MAS gradually increased and at 8 h reached a level that was comparable with that of 0 h at 8 h. The mean MAS (SD) was 6.2 (1.2) at 0 h, 3.3 (1.0) at 1 h, 2.8 (1.7) at 2 h, 3.0 (1.7) at 4 h, and 5.7 (0.5) at 8 h. In contrast, sham-operated control mice exhibited no spasticity before or after the administration of baclofen (Fig. 1b). These results demonstrated that the intraperitoneal administration of baclofen transiently exerted antispastic effects on only the spastic mice and that 8 h was a sufficient duration to examine the functional effect of baclofen in our experiments.

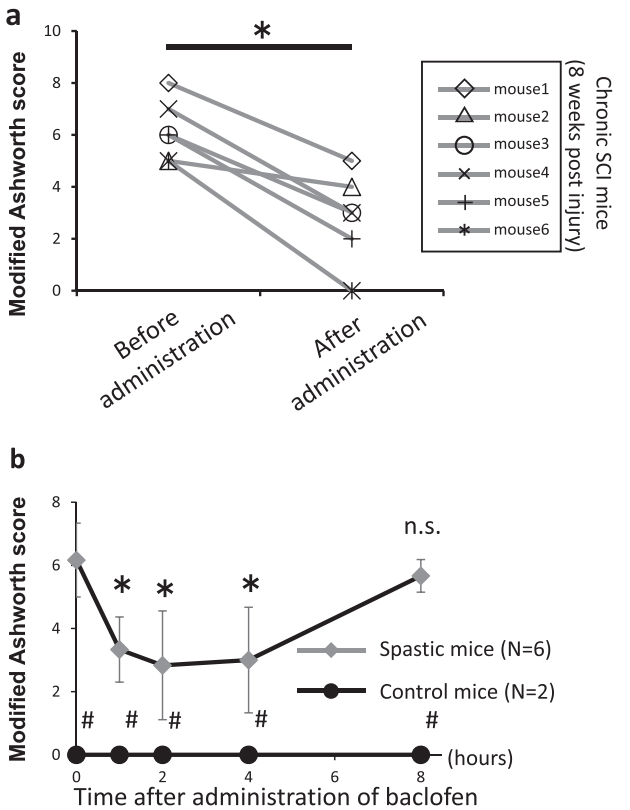

Fig. 1 The intraperitoneal administration of baclofen effectively ameliorated the severity of spasticity in chronic SCI mice. a The severity of spasticity was evaluated by the modified Ashworth score (MAS) before and at 2 h after the intraperitoneal administration of baclofen ($n = 6$). All SCI mice exhibited various MASs at 8 weeks post injury. In each mouse, the MAS was significantly decreased after the administration of baclofen ($n = 6$). *$P < 0.05$, Wilcoxon's rank test. **b** The time-course of the changes in MAS was evaluated until 8 h after the administration of baclofen. In the spastic mice, the MAS decreased immediately and bottomed at 2 h post administration. At 8 h post administration, the MAS was not significantly different from that before administration. In the control mice, the MAS did not change after the administration of baclofen. *$P < 0.05$, Dunnett's test in comparison with the MAS before administration (*) and a one-way ANOVA with a post hoc Tukey–Kramer test between each group (#). Error bars indicate the SD.

The antispastic influence of baclofen on the locomotor function in mice with chronic SCI

To elucidate the antispastic influence of baclofen on the locomotor function, we also assessed the BBB/BMS values at 0, 1, 2, 4, and 8 h. Interestingly, both locomotor scores significantly decreased at 1 h in comparison with that at preadministration and bottomed at 2 h. Thereafter, these scores gradually recovered and at 8 h reached a level that

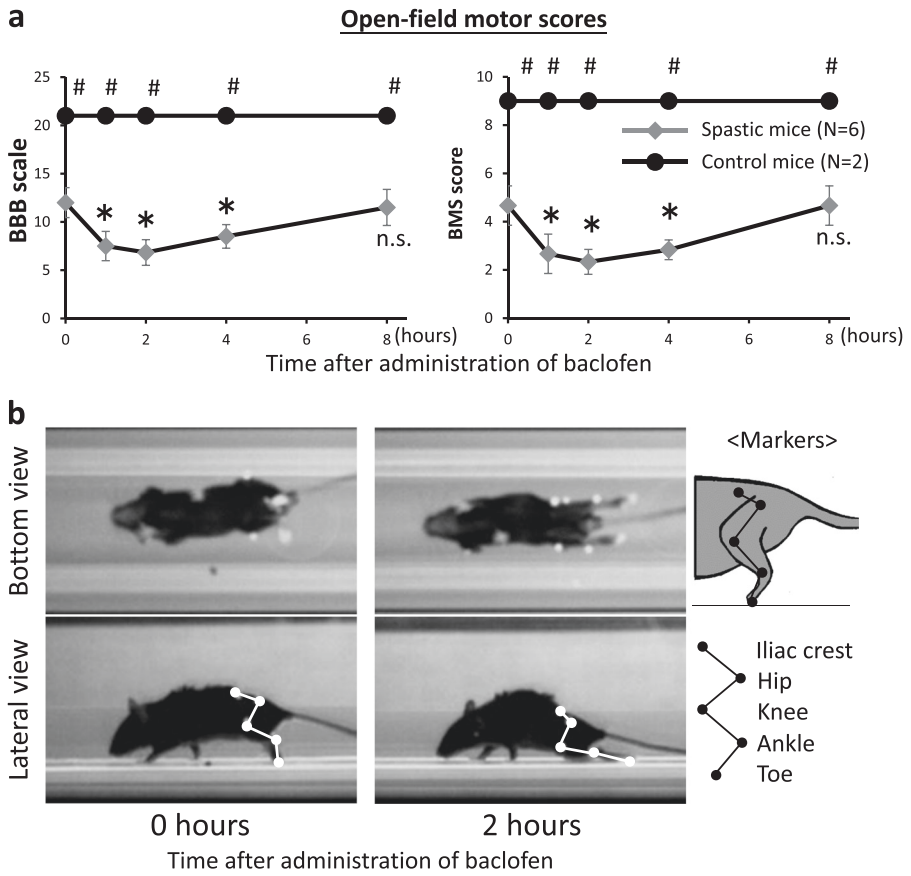

Fig. 2 The antispastic influence of intraperitoneally administered baclofen was associated with the locomotor dysfunction of chronic SCI mice. a The time-course change of the locomotor function after the administration of baclofen was evaluated by the open field score. In spastic mice, both the BBB and BMS values decreased immediately and bottomed at 2 hours post administration. At 8 hours post administration, the MAS was not significantly different from that before the administration of baclofen. In the control mice, the MAS did not change after the administration of baclofen. $*P < 0.05$, Dunnett's test in comparison with the MAS before administration (*) and a one-way ANOVA with a post hoc Tukey–Kramer test between each group (#). Error bars indicate the SD. **b** Representative photographs of spastic mice performing overground walking before and after the administration of baclofen. Images were captured from the bottom and lateral sides. White dots indicate the markers on the iliac crest, hip, knee, ankle, and toe.

was comparable with that before the administration of baclofen. The mean BBB (SD) was 12 (1.5) at 0 h, 7.5 (1.5) at 1 h, 6.8 (1.3) at 2 h, 8.5 (1.2) at 4 h, and 12 (1.9) at 8 h. The mean BMS (SD) was 4.7 (0.82) at 0 h, 2.7 (0.82) at 1 h, 2.3 (0.52) at 2 h, 2.8 (0.41) at 4 h, and 4.6 (0.82) at 8 h. In contrast, sham-operated mice did not exhibit any motor disability before or after the administration of baclofen (Fig. 2a, b). These results demonstrated that the antispastic influence of baclofen was only associated with a transient deterioration of the locomotor dysfunction in the spastic mice and that the spinal spasticity effectively contributed to the locomotor function in the SCI mice.

Spasticity-dependent ambulation in a chronic SCI patient

Similarly, we report a representative case involving a chronic SCI patient who transiently exhibited an impaired ambulatory function after the administration of baclofen. The patient was a 52-year-old woman who suffered from tetraplegia due to cervical SCI and who had undergone orthopedic surgery in our institution 3 years previously. After intense rehabilitation, she had exhibited substantial recovery in her ambulation ability with a cane and orthosis. However, incomplete paralysis remained and her American Spinal Injury Association impairment scale was D. One year before this study, she therefore revisited our institution due to severe spasticity of the bilateral legs (MAS: 4), which caused spasticity-related pain and involuntary muscle spasms. Since the effect of oral antispastic medications had been insufficient due to side effects, we proposed optional antispastic therapy using the continuous intrathecal infusion of baclofen. We then investigated the antispastic effects induced by the intrathecal infusion of baclofen (50 μg; Gabalon® intrathecal injection 0.05%; Daiichi Sankyo Co, Ltd, Japan). Before the administration of baclofen, she was

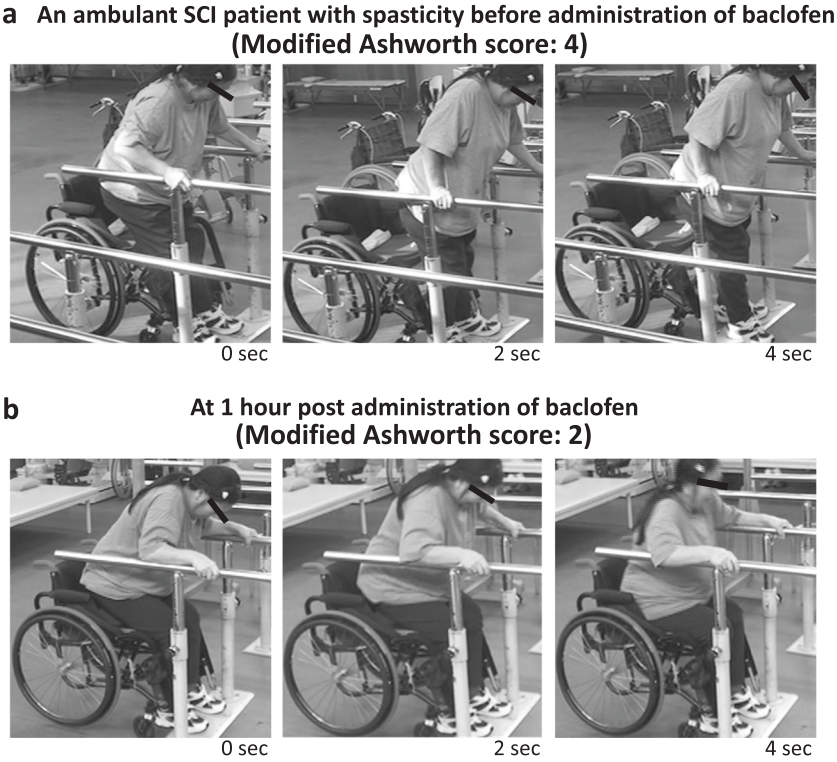

Fig. 3 The antispastic influence of intrathecally administered baclofen was associated with ambulation disability in a chronic SCI patient. The effect of baclofen on ambulation ability in parallel-bar walking was evaluated in a patient with chronic SCI. **a** Before the intrathecal administration of baclofen, she could stand up and walk with spasticity. **b** After the administration of baclofen, although the severity of her spasticity was ameliorated, she could not even stand up. The antispastic effect of baclofen disappeared by 4 hours post administration

able to walk between parallel bars (Fig. 3a). However, after the administration of a minimal dose of baclofen, she exhibited motor weakness in her lower extremity and became unable to even stand, although her spasticity was successfully ameliorated (MAS: 2) (Fig. 3b). Her ambulatory function recovered as the drug wore off. This result suggests that her spinal spasticity had beneficially contributed to ambulation and standing.

Discussion

In this study, baclofen effectively ameliorated spasticity; however, it unexpectedly exacerbated the locomotor disability in both SCI mice and a human patient, suggesting that spasticity may have beneficial aspects for ambulatory ability after SCI.

During normal walking, the spinal cord centrally orchestrates a sequence of appropriate reflexes in the muscles of the lower limbs. Once one muscle is passively extended, the afferent monosynaptic Ia fibers from the muscle are excited. Since the monosynaptic Ia fibers directly connect to the motor neurons innervating the muscle itself, the tonus of the muscle is physiologically maintained [5]. On the other hand, since the afferent Ia fibers also connect to the motor neurons innervating the antagonist muscle via inhibition interneurons in the spinal cord, the tonus of the antagonist muscle is contrarily weakened [6]. The former is termed the muscle stretch reflex and the latter is termed the reciprocal Ia inhibition; both are essential spinal reflexes for ambulation.

In addition to the tonus of muscles, the stepping rhythm of the lower limbs is regulated by the spinal cord. This mechanism was first reported as the "half-center hypothesis" by Graham Brown prior to 1920 [17]. The "half-center" is composed of a flexor half-center, an extensor half-center, and reciprocally inhibiting interneurons [17]. For several decades after the report, it was hypothesized that the stepping rhythm was generated by the above spinal reflex alone [17]. Subsequently, Brown et al. and Lundberg et al. developed the hypothesis that the spinal cord possessed the spinal centers capable of intrinsically instigating flexor and extensor excitations without descending or sensory inputs [17]. In recent reports, much emphasis has been placed on this spinal half-center interneuronal circuitry as a central pattern generator [17]. Thus, the appropriate regulation of these reflexes by the interneuronal circuitry in the spinal cord is considered to be essential for ambulation [18].

Soon after SCI, supraspinal inhibitory control, particularly that of disynaptic reciprocal inhibition, is reported to be significantly reduced. Thus, in the pathology of SCI, the central pattern generator caudal to the spinal lesions becomes hyperexcited [19]. However, in the chronic phase of SCI, whether the central pattern generator is hyperactive or hypoactive remains controversial. In previous studies on spastic SCI patients, the reciprocal Ia inhibition of ankle plantarflexor motor neurons was reported to be reduced, and this was reported to lead to foot drop, causing disability in

ambulation [20]. Thus, hyperexcitability in the lower-limb muscle stretch reflex is, at least based on the present findings, considered to be a central component in the mechanism of spinal spasticity.

The antispastic drug baclofen is a centrally acting GABA analog. It binds to GABA receptors at the presynaptic terminal and inhibits excessive muscle stretch reflex [21]. In this study, the administration of baclofen immediately and efficiently reduced the spasticity in spastic mice. However, the antispastic effect was transient, lasting 8 hours in mice, and 4 hours in a human patient (Figs. 1 and 3). Previous studies also reported similar results in humans; the first effect occurred within 1 hour, the maximum effect occurred after 2–4 hours, and the total effect lasted for 8 hours after the intrathecal administration of baclofen [22]. Thus, the clinical application of baclofen is usually performed using a continuous infusion pump system.

Regarding the baclofen dose, we administered the lowest effective dose to the spastic mice in this study. In previous reports, the dose of baclofen administered for screening tests was 50–100 μg for adult patients and 0.5 μg for mice [23]. In our preliminary experiments in which the dose of baclofen ranged from 0 to 1 μg/mouse, the intraperitoneal administration of normal saline did not have any effect on the locomotor function and spasticity, and dose of >0.3 μg significantly reduced the MAS of SCI mice (data not shown). This result negated any concerns about the potential for gut pain to inhibit locomotion and gut pain being a reported symptom after SCI [24]. We therefore administered baclofen (0.3 μg) and assessed both the BBB/BMS and MAS until 8 hours post administration.

In this study, the locomotor function of the control sham-operated mice was not affected by the administration of baclofen, which suggested that baclofen could selectively act on spastic limbs (Fig. 2). This result is consistent with the results of a previous study that reported that no obvious motor weakness was observed on the normal side of hemispastic patients after the intrathecal administration of baclofen [25]. Although the mechanism of this selective antispastic effect of baclofen remains unclear, we hypothesize that pathological changes in the sensitivity of GABA receptors might be involved. In fact, Gerard et al. reported that altered supraspinal input after CNS injury resulted in changes in the sensitivity of GABA receptors to baclofen [26]. Considering that the number of GABAergic cells is quickly recovered both rostral and caudal to the lesion after SCI [27], the spinal spasticity was attributed to the decreased sensitivity of the GABA receptors in the spinal cord, rather than the decreased number of GABAergic cells. Thus, the administration of baclofen effectively exerted GABAergic-supraspinal inhibition in the spastic mice but not the control mice.

In the SCI patient in this study, the severity of spasticity was effectively ameliorated whereas the difficulty in ambulation was exacerbated after the administration of baclofen (Fig. 3), suggesting that human spasticity had also beneficial effects on the lower-limb function. In ambulatory spastic patients, both the flexor and extensor muscles are pathologically co-activated, termed co-contraction, which results in the inflexibility of the lower limbs. Despite the joint inflexibility, this pathological activation of the antigravity muscles, such as the femoral quadriceps, hamstrings, and gastrocnemius, is reported to be useful for their body weight loading during ambulation/standing and preventing muscular atrophy [28]. In contrast to the antigravity muscles, nonantigravity muscles gradually fall into in degenerative atrophy (muscle fiber substitution with adipose and fibrotic tissue) in such conditions [29]. Thus, the dependency on antigravity-muscle spasticity would be significantly increased in ambulatory SCI patients and the transient reduction of spasticity by the administration of baclofen could significantly impair their ambulatory function.

One limitation of this study is that the present findings are only applicable to patients whose spasticity contribute to ambulatory function. In fact, factors leading to spasticity are reported to be complex; for example, even after the surgical treatment of spasticity, remaining spasticity can gradually worsen and limit the range of motion of joints in some cases [30]. Thus, once muscle adaptation occurs, the reduction of spasticity is unlikely to detrimentally influence the ambulatory function. The present findings highlight the importance of determining the contribution of spasticity to the ambulation function in each spastic patient in order to ameliorate symptoms associated with spasticity.

Conclusion

We demonstrated that spasticity has beneficial aspects on the locomotor function. It is important to note that in chronic SCI patients, antispastic therapy may be associated with a risk of impairing the preserved ambulation ability.

Data availability

All data generated or analyzed during this study are included in this published article.

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Author contributions SY designed the studies, prepared thoracic contusion SCI mice and administered baclofen to the mice, performed the statistical analysis, and drafted the manuscript. KY, KK, and TS performed the BBB/BMS and MAS data collection. MT and DK supervised the overall project and gave technical advice. TM obtained informed consent from the chronic SCI patient. YM and YN designed the studies and supervised the overall project. SO designed the studies, supervised the overall project, and performed the final manuscript preparation. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement All surgical procedures and experimental manipulations were approved by the Committee of Ethics on Animal Experimentation in the Faculty on Medicine, our university (A28-251-0). Experiments were conducted under the control of the Guidelines for Animal Experimentation.

Informed consent Written informed consent for the publication of information and images was provided by the chronic SCI patient.

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References

1. Lance JW. The control of muscle tone, reflexes, and movement: Robert Wartenbeg Lecture. Neurology. 1980;30:1303.
2. Lance JW. What is spasticity? Lancet. 1990;335:606.
3. Kirshblum S. Treatment alternatives for spinal cord injury related spasticity. J Spinal Cord Med. 1999;22:199–217.
4. Norton JA, Bennett DJ, Knash ME, Murray KC, Gorassini MA. Changes in sensory-evoked synaptic activation of motoneurons after spinal cord injury in man. Brain. 2008;131:1478–91.
5. Gracies JM. Pathophysiology of spastic paresis. I: paresis and soft tissue changes. Muscle Nerve. 2005;31:535–51.
6. Gracies JM. Pathophysiology of spastic paresis. II: emergence of muscle overactivity. Muscle Nerve. 2005;31:552–71.
7. Schindler-Ivens S, Shields RK. Low frequency depression of H-reflexes in humans with acute and chronic spinal-cord injury. Exp Brain Res. 2000;133:233–41.
8. Kheder A, Nair KP. Spasticity: pathophysiology, evaluation and management. Pract Neurol. 2012;12:289–98.
9. Meythaler JM, Clayton W, Davis LK, Guin-Renfroe S, Brunner RC. Orally delivered baclofen to control spastic hypertonia in acquired brain injury. J Head Trauma Rehabil. 2004;19:101–8.
10. Knutsson E, Lindblom U, Mårtensson A. Plasma and cerebrospinal fluid levels of baclofen (Lioresal) at optimal therapeutic responses in spastic paresis. J Neurol Sci. 1974;23:473–84.
11. Teasell RW, Mehta S, Aubut JA, Foulon B, Wolfe DL, Hsieh JT, et al. A systematic review of pharmacologic treatments of pain after spinal cord injury. Arch Phys Med Rehabil. 2010;91:816–31.
12. Hara M, Kobayakawa K, Ohkawa Y, Kumamaru H, Yokota K, Saito T, et al. Interaction of reactive astrocytes with type I collagen induces astrocytic scar formation through the integrin-N-cadherin pathway after spinal cord injury. Nat Med. 2017;23:818–82.
13. Akpinar P, Atici A, Ozkan FU, Aktas I, Kulcu DG, Sarı A, et al. Reliability of the modified Ashworth Scale and modified Tardieu Scale in patients with spinal cord injuries. Spinal Cord. 2017;55:944–9.
14. Dong HW, Wang LH, Zhang M, Han JS. Decreased dynorphin A (1-17) in the spinal cord of spastic rats after the compressive injury. Brain Res Bull. 2005;67:189–95.
15. Basso DM, Beattie MS, Bresnahan JC. A sensitive and reliable locomotor rating scale for open field testing in rats. J Neurotrauma. 1995;12:1–21.
16. Basso DM, Fisher LC, Anderson AJ, Jakeman LB, McTigue DM, Popovich PG. Basso Mouse Scale for locomotion detects differences in recovery after spinal cord injury in five common mouse strains. J Neurotrauma. 2006;23:635–59.
17. Stuart DG, Hultborn H. Thomas Graham Brown (1882–1965), Anders Lundberg (1920-), and the neural control of stepping. Brain Res Rev. 2008;59:74–95.
18. Gossard JP, Delivet-Mongrain H, Martinez M, Kundu A, Escalona M, Rossignol S. Plastic changes in lumbar locomotor networks after a partial spinal cord injury in cats. J Neurosci. 2015;35:9446–55.
19. Nielsen JB, Crone C, Hultborn H. The spinal pathophysiology of spasticity-from a basic science point of view. Acta Physiol. 2007;189:171–80.
20. Boorman G, Hulliger M, Lee RG, Tako K, Tanaka R. Reciprocal Ia inhibition in patients with spinal spasticity. Neurosci Lett. 1991;127:57–60.
21. Penn RD, Kroin JS. Intrathecal baclofen alleviates spinal cord spasticity. Lancet. 1984;1:1078.
22. Heetla HW, Proost JH, Molmans BH, Staal MJ, van Laar T. A pharmacokinetic-pharmacodynamic model for intrathecal baclofen in patients with severe spasticity. Br J Clin Pharmacol. 2016;81:101–12.
23. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm. 2016;7:27–31.
24. Siddall PJ, Loeser JD. Pain following spinal cord injury. Spinal Cord. 2001;39:63–73.
25. Meythaler JM, Guin-Renfroe S, Brunner RC, Hadley MN. Intrathecal baclofen for spastic hypertonia from stroke. Stroke. 2001;32:2099–109.
26. Francisco Gerard E, Boake Corwin. Improvement in walking speed in poststroke spastic hemiplegia after intrathecal baclofen therapy: a preliminary study. Arch Phys Med Rehabil. 2003;84:1194–9.
27. Romaus-Sanjurjo D, Valle-Maroto SM, Barreiro-Iglesias A, Fernández-López B, Rodicio MC. Anatomical recovery of the GABAergic system after a complete spinal cord injury in lampreys. Neuropharmacology. 2018;131:389–402.
28. Krawetz P, Nance P. Gait analysis of spinal cord injured subjects: effects of injury level and spasticity. Arch Phys Med Rehabil. 1996;77:635–8.
29. Kern H, Hofer C, Mödlin M, Mayr W, Vindigni V, Zampieri S, et al. Stable muscle atrophy in long-term paraplegics with complete upper motor neuron lesion from 3- to 20-year SCI. Spinal Cord. 2008;46:293–304.
30. O'Dwyer NJ, Ada L, Neilson PD. Spasticity and muscle contracture following stroke. Brain. 1996;119:1737–49.