Bilateral hyperexcitability of thalamic VPL neurons following unilateral spinal injury in rats

Young Seob Gwak · Hee Kee Kim · Hee Young Kim · Joong Woo Leem

Abstract In the present study, we have examined whether spinal hemisection injury induces changes in the electrophysiological properties of thalamic ventral posterolateral (VPL) neurons in rats. Male Sprague–Dawley rats were subjected to unilateral spinal cord injury by transverse hemisection at the T13 spinal segment. Four weeks after the T13 spinal hemisection, the injured rats displayed robust allodynic behaviors on both sides of hindpaws compared to sham controls ($P < 0.05$). Extracellular recordings taken 4 weeks after the hemisection revealed that wide dynamic range (WDR) neurons had significantly increased spontaneous and brush-, pressure-, and pinch-evoked activities, respectively, on both sides of the thalamic VPL regions ($P < 0.05$). In contrast, low threshold (LT) neurons showed only an increase in the brush-evoked activity compared to sham controls ($P < 0.05$). However, afterdischarge activity in both types of neurons showed no changes. In addition, both sides of the thalamic VPL regions showed higher incidences of WDR neurons. In conclusion, our data demonstrate that spinal unilateral injury induces bilaterally increased evoked activity in thalamic VPL neurons.

Keywords Central neuropathic pain · Hyperexcitability · Spinal cord injury · Ventral posterolateral

Introduction

Traumatic thoracic spinal cord injury (SCI) produces neuronal hyperexcitability at-level and below-level (lumbar) regions in the spinal cord [1, 2]. In vivo electrophysiological studies demonstrate that hyperexcitable neurons show enhanced response properties, including evoked and spontaneous activities and afterdischarges in spinal dorsal horn neurons following SCI [3–5]. Neuronal hyperexcitability triggers sensitizations of spinal dorsal horn neurons followed by the development and the maintenance of central neuropathic pain-like outcomes, such as mechanical allodynia and hyperalgesia [3, 6].

Spinal dorsal horn neurons are second-order neurons involved in the transmissions of somatosensory sensations, forwarding the information to third-order neurons, the thalamic ventral posterolateral (VPL) neurons. In vivo electrophysiological studies using rodent SCI models have recently demonstrated that spinal dorsal horn neurons can display distinct changes in their response property. For example, low thoracic spinal hemisection injury induces bilateral hyperexcitability in lumbar (below-level region) spinal dorsal horn neurons [1, 7]. Spinal contusion injury also induces neuronal hyperexcitability in the at-level region after SCI [2]. In addition, neuronal hyperexcitability is well correlated with central neuropathic pain-like behaviors, such as mechanical allodynia and hyperalgesia. Taken together, electrophysiological and behavioral studies suggest that neuronal hyperexcitability is a critical contributory factor to the central neuropathic pain mechanism following SCI.
Spinal blocks do not completely attenuate central neuropathic pain-like outcomes following SCI [8]. In addition, SCI initiates electrophysiological events and reorganizations in supraspinal regions that correlate well with central neuropathic pain-like behaviors [9]. These data suggest that SCI primarily produces neuronal hyperexcitability in the spinal dorsal horn but that changes in neuronal properties extend up to the supraspinal level, especially in the thalamic VPL region. Published results from animal and clinical studies suggest supraspinal mechanisms for the manifestation of chronic central neuropathic pain following SCI [8, 10–12], but the electrophysiological mechanism is not yet clear.

Data from our earlier studies consistently demonstrated bilateral hyperexcitability of spinal dorsal horn neurons and chronic neuropathic pain behaviors following spinal hemisection injury [1, 3]. In the study reported here, we examined whether low thoracic spinal hemisection injury induces changes in the electrophysiological properties in thalamic VPL regions using the in vivo extracellular recording technique. To compare the neuronal activity property of thalamic VPL neurons following spinal hemisection, we tested spontaneous, afterdischarges, and mechanically evoked activities, respectively.

Materials and methods

Spinal cord injury

Spinal cord injury (25 rats) was achieved by transverse T13 hemisection in young adult Sprague–Dawley rats (225–250 g) under masked enflurane anesthesia (induction 3% and maintenance 2%). Briefly, after laminectomy of the T11–T12 spinal vertebral segments, the spinal cord was hemisection, dorsal to ventral, at the T13 spinal vertebral level, especially in the thalamic VPL region. Published results from animal and clinical studies suggest supraspinal mechanisms for the manifestation of chronic central neuropathic pain following SCI [8, 10–12], but the electrophysiological mechanism is not yet clear.

Data from our earlier studies consistently demonstrated bilateral hyperexcitability of spinal dorsal horn neurons and chronic neuropathic pain behaviors following spinal hemisection injury [1, 3]. In the study reported here, we examined whether low thoracic spinal hemisection injury induces changes in the electrophysiological properties in thalamic VPL regions using the in vivo extracellular recording technique. To compare the neuronal activity property of thalamic VPL neurons following spinal hemisection, we tested spontaneous, afterdischarges, and mechanically evoked activities, respectively.

Measurement of mechanical allodynia

To evaluate the mechanical allodynic behaviors following spinal hemisection, we measured the 50% withdrawal threshold in response to mechanical stimuli in both the contralateral (uninjured) side and the ipsilateral (injured) side of hindpaw, respectively. Briefly, individual rats were housed in behavior test plastic cages (8 × 8 × 24 cm) and acclimated for 30 min to avoid the stress induced by the change in environment. Mechanical stimuli were given von Frey filaments (Stoelting, Wood Dale, IL), which were sequentially applied (increasing or decreasing) to the glabrous surface of the paw for a total of six applications. The first stimulus was 4.31 log unit von Frey filament; there was a 10-s interstimulus interval (a series of von Frey filaments log unit: 3.61, 3.84, 4.08, 4.31, 4.56, 4.74, 4.93, 5.18). The final calculation of 50% withdrawal mechanical threshold was determined by the formula log (50% threshold) = Xf + κδ, where Xf was the value of the final von Frey filament (log unit), κ was the correction factor (from calibration table), and δ was the mean difference of log units between stimuli. The 18 g pressure of the 50% threshold was selected as the cut-off value [14, 15].

Electrophysiological experiment

Animal preparation

After 4 weeks of spinal hemisection (according to behavioral outcomes), the rats administered anesthesia in the form of an injection of sodium pentobarbital (50 mg/kg, intraperitoneal). A tracheal cannula for artificial ventilation (Ventilator; CWE, Ardmore, PA) from room air and a jugular vein cannula for supplemental paralysis with pancuronium bromide (2–4 mg/kg/h) were inserted. The head of the rat was framed onto a stereotaxic apparatus, and a craniotomy was performed to expose the surface of brain. The status of the rat was monitored by end-tidal CO2 concentration using a carbon dioxide analyzer (3.5–4.5%; CWE). Body temperature was monitored using a thermometer probe inserted into the esophagus and maintained at 37°C using a homeothermic blanket control unit (Harvard Apparatus, South Natick, MA) under the ventral surface of the abdomen.

Electrophysiology protocols

In vivo extracellular recordings of thalamic VPL neurons (2.4–3.0 mm posteriorly from the bregma; 2.8–3.7 mm laterally from the midline; 4.5–5.9 mm from the brain surface; Fig. 2, Table 1) were made using a tungsten electrode (5 MΩ). Based on data from previous studies, the thalamic VPL neurons were classified into three types: low threshold (LT; low threshold mechanoreceptive), high

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threshold (HT), and wide dynamic range (WDR) neurons [16]. The neuronal responses of WDR neurons display graded activity in response to increased intensities of mechanical stimuli, while the LT and HT neurons display intense responses in response to non-noxious and noxious stimuli, respectively. The recording of the ipsilateral side (hemisected side) thalamic VPL neurons was performed by applying mechanical stimuli to the contralateral side of the hindpaw, and that of the contralateral (uninjured) side thalamic VPL neurons was performed by applying mechanical stimuli to the ipsilateral side of the hindpaw. The mechanical stimuli were applied only to the glabrous skin of the hindpaw (mainly toes) for 10 s and included: (1) brushing the receptive field with a camel hair brush (brush); (2) sustained application of the receptive field with a large clamp (ROBOZ) that produced a sense of firm pressure (pressure); (3) sustained application of receptive field with a small clamp (ROBOZ) that produced a distinctly painful sensation (pinch). Following the isolation of a single neuron, the neuronal activity was amplified (DAM80; WPI, Sarasota, FL), filtered, and displayed on an oscilloscope. The output signals were also fed into a data acquisition system (CED 1401 plus; Cambridge Electronic Design, Cambridge, UK) via a window discriminator (WPI). The real time recording of the peristimulus histogram and waveforms of activity was displayed as the number of spikes per second using the spike2 software program. Following the isolation of a single neuron’s activity, spontaneous activity was recorded for 20 s before brush stimulation. After the pinch stimulation, afterdischarge activity was recorded for 30 s without any stimulation. The mean values of mechanically evoked and afterdischarge activities were subtracted by the mean value of the spontaneous activity because there were significant differences between rats with hemisection and sham controls with respect to spontaneous activity.

Statistical analysis

Statistical analysis of the behaviors and electrophysiology results was performed using the two-way repeated measures analysis of variance (ANOVA) with time as a factor, followed by the Duncan’s test for multiple comparisons and unpaired t test using the SigmaStat program (ver 3.1). An alpha level of significance was set at 0.05 for all statistical tests. Data are expressed as mean ± standard error (SE).

Results

Mechanical allodynia

Prior to spinal hemisection, mean withdrawal thresholds of those rats who subsequently underwent hemisection (17.4 ± 0.3 g-contralateral and 17.5 ± 0.3 g-ipsilateral) were not significantly different from those of sham controls (16.4 ± 0.7 g-contralateral and 17.2 ± 0.4 g-ipsilateral). However, mean withdrawal thresholds of rats with hemisection on post-operative day (POD) 28 (4.2 ± 0.2 g-contralateral and 4.5 ± 0.4 g-ipsilateral) were significantly different from those of sham controls (16.9 ± 0.6 g-contralateral and 16.4 ± 0.6 g-ipsilateral) and prior to hemisection (P < 0.05; Fig. 1).

Thalamic VPL recordings and proportional changes of neuronal cell type distributions

A total of 89 thalamic VPL neurons were sampled, including 31 neurons from the 10 sham rats and 58 neurons from the 25 hemisected rats. Figure 2 shows the diagram of thalamic VPL recordings following spinal hemisection, and Table 1 shows the locations of sampled neurons in both sham controls and hemisected rats. In sham controls, the distribution of the thalamic neurons were 51.6% LT (n = 16), 9.7% HT (n = 3), and 38.7% WDR (n = 12). In rats with hemisection, however, 34.5 (n = 10, ipsilateral) and 44.8% (n = 13, contralateral) was LT neurons, and 65.5 (n = 19, ipsilateral) and 55.2% (n = 16, contralateral) was WDR neurons (Table 1). High threshold neurons

![Fig. 1 Time courses of mechanical allodynic behaviors following spinal hemisection. After spinal cord injury (n = 20), injured (ipsilateral, ipsil) and uninjured (contralateral, contra) sides of hindpaws showed significant decreases of paw withdrawal thresholds in response to von Frey filaments stimuli compared to sham controls (n = 10). However, the side-by-side comparison did not reveal any significant difference. Asterisk Significant difference (P < 0.05) between sham control and contralateral side. #Significant difference (P < 0.05) between sham control and ipsilateral side. Values are given as the mean ± standard error.](image)
were not respectively observed in rats with hemisection, although we did record three HT neurons in sham controls.

The activity of WDR neurons

Figure 3a shows waveforms of activity from WDR neurons in both sham controls and hemisected rats. The mean spontaneous activity of thalamic VPL WDR neurons ($n = 12$) in sham controls was $2.0 \pm 0.6$ spikes/s. However, rats with hemisection showed significant increases in mean spontaneous activity in both ipsilateral ($4.9 \pm 0.7$ spikes/s, $n = 19$, $P < 0.05$) and contralateral ($5.0 \pm 0.7$ spikes/s, $n = 16$, $P < 0.05$) sides compared to sham controls (Fig. 3b). In sham controls, the mean activity of WDR neurons was $8.6 \pm 1.3$, $14.2 \pm 1.5$, and $17.4 \pm 1.8$ spikes/s in response to brush, pressure, and pinch stimuli, respectively. However, rats with hemisection showed significantly increased evoked activity in both contralateral ($20.2 \pm 1.6$, $24 \pm 2.0$, and $26.7 \pm 2.2$ spikes/s, respectively) and ipsilateral ($23 \pm 1.6$, $21 \pm 1.4$ and $24.0 \pm 1.5$ spikes/s, respectively) sides compared to sham controls ($P < 0.05$, Fig. 3c). With respect to afterdischarge activity, the mean afterdischarge activity of thalamic VPL WDR neurons in sham controls was $6.67 \pm 1.93$ spikes/s. After hemisection, the mean afterdischarge activity of thalamic VPL WDR neurons in rats with hemisection was $5.68 \pm 1.21$ spikes/s (ipsilateral) and $7.58 \pm 1.39$ spikes/s (contralateral); these values were not significantly different from those of sham controls (Fig. 3d).

The activity of LT neurons

Figure 4a shows waveforms of activity from LT neurons in both sham controls and hemisected rats. The mean spontaneous activity of thalamic VPL LT neurons ($n = 16$) in sham controls was $1.6 \pm 0.3$ spikes/s. However, the mean spontaneous activity of LT neurons in rats with hemisection was not significantly different in either the ipsilateral ($2.3 \pm 0.7$ spikes/s, $n = 10$) or contralateral ($2.2 \pm 0.3$ spikes/s, $n = 13$) side (Fig. 4b). In sham controls, the mean activity of LT neurons in response to brush stimuli was $9.17 \pm 0.86$ spikes/s. In comparison, in rats with hemisection, the mean activity of LT neurons was $21.9 \pm 1.5$ spikes/s (ipsilateral, $P < 0.05$) and $22.3 \pm 3.1$ spikes/s (contralateral, $P < 0.05$), although the activities of LT neurons in response to pressure and pinch stimuli were not significantly different from those of sham controls (Fig. 4c).

In afterdischarge activity, the mean afterdischarge activity of thalamic VPL LT neurons in sham controls was $0.55 \pm 0.29$ spikes/s. After hemisection, the mean afterdischarge activity of thalamic VPL LT neurons was $0.69 \pm 0.26$ spikes/s (ipsilateral) and $0.58 \pm 0.19$ spikes/s (contralateral); these activity were not significantly different from that of sham controls (Fig. 4d).

The comparison of spontaneous activity from HT neurons was excluded because we did not observe HT neurons in the hemisection group.

Discussion

The results of our present study demonstrate that low thoracic spinal hemisection produced mechanical allodynic behaviors in both sides of hindpaws and increases in mechanically evoked activity as well as altered distributions of neurons in thalamic VPL neurons. As such, they suggest that unilateral spinal injury causes bilaterally increased excitability of thalamic VPL neurons in rats.

It is well known that spinal hemisection produces mechanical allodynic behaviors in both sides of hindpaws and hyperexcitability in the lumbar dorsal horn neurons [1, 17]. However, it is very interesting that spinal hemisection induces hyperexcitability in bilateral thalamic VPL.
Table 1 Recording sites and distributions of sampled neurons in thalamic ventral posteriorlateral regions following T13 spinal hemisection

| Recording site (mm) | Distributions (%) |
|---------------------|-------------------|
| From the bregma<sup>a</sup> | From the midline<sup>b</sup> | From the surface<sup>c</sup> |
| **Sham (numbers)** | | | |
| LT (16) | 2.7 ± 0.142 | 3.2 ± 0.06 | 5.3 ± 0.08 | 51.61 |
| HT (3) | 2.2 ± 0.321 | 3.5 ± 0.145 | 5.8 ± 0.152 | 9.68 |
| WDR (12) | 2.3 ± 0.109 | 3.4 ± 0.05 | 5.5 ± 0.108 | 38.91 |
| **Hemisection (numbers)** | | | |
| Contralateral | | | | |
| LT (13) | 2.8 ± 0.04 | 3.3 ± 0.05 | 5.3 ± 0.08 | 44.83 |
| HT (–) | – | – | – | 0 |
| WDR (16) | 2.8 ± 0.05 | 3.2 ± 0.06 | 5.1 ± 0.06 | 55.17 |
| Ipsilateral | | | | |
| LT (10) | 2.9 ± 0.04 | 3.1 ± 0.04 | 5.5 ± 0.08 | 34.48 |
| HT (–) | – | – | – | 0 |
| WDR (19) | 2.8 ± 0.03 | 3.1 ± 0.05 | 5.3 ± 0.06 | 65.52 |

For the recording of thalamic ventral posteriorlateral (VPL) neurons, 31 neurons from sham controls were sampled and 58 neurons from hemisected rats. In sham controls, there were large populations of low threshold (LT) neurons (51.6%), whereas rats with hemisection had large populations of wide dynamic range (WDR) neurons in both ipsilateral (65.5%) and contralateral (55.2%) sides. High threshold (HT) neurons were not observed in rats with hemisection, although three HT neurons were recorded in sham controls.

<sup>a</sup> Posteriorly from the bregma

<sup>b</sup> Laterally from the midline

<sup>c</sup> Depth from the surface

Fig. 3 Comparison of neuronal activity of thalamic VPL WDR neurons following T13 spinal hemisection. **a** Typical waveforms of WDR neurons in thalamic VPL regions from both sham (top) and hemisected rat (bottom). **b** In terms of background activity (20 s), both sides of thalamic VPL WDR neurons show significant differences compared to sham controls. **c** After hemisection, brush-, pressure-, and pinch-evoked activity is significantly different from those of sham controls, respectively. **d** In terms of afterdischarge activity, both sides of thalamic VPL WDR neurons were not significantly different compared to sham controls. Values are graphed as means ± SE. *P < 0.05
neurons. In this study, we examined neuronal activity in thalamic VPL regions of rats 4 weeks after they had undergone hemisection because this time point showed robust mechanical allodynic behaviors after hemisection. Thalamic VPL neurons receive somatosensory sensation, especially nociceptive, via spinothalamic tracts (STTs), which is decussated in the spinal cord. Because spinal hemisection mechanically destroys STTs on the injured side of the spinal cord, the thalamic VPL neurons of the ipsilateral (injured) side did not recognize somatosensory sensation, which originated from the receptive field located in the hindpaw of the contralateral side. The presence of VPL hyperexcitability in the contralateral side (uninjured side and the receptive field is located in the ipsilateral side, i.e. the left hindpaw) is then easily hypothesized. Spinal hemisection induces sensitization of spinal dorsal horn neurons via the loss of endogenous inhibitory pathways and activation of glutamate receptors in the dorsal horn [3, 18]. The sensitization of spinal dorsal horn neurons contributes to the development and the maintenance of enhanced nociceptive transmissions to thalamic VPL neurons.

However, such postulations of VPL hyperexcitability in the ipsilateral side (hemisected side and the receptive field is located in the contralateral side, i.e. the right hindpaw) are not as clear. The first possible explanation is the intensive barrage of impulses caused by the direct traumatic SCI trigger activation of primary afferent fibers, followed by increased release of pain-mediating substances, such as excitatory amino acid and neuropeptides, in the thalamus. For example, high concentrations of glutamate trigger activation of NMDA receptors in the thalamus, followed by the massive influx of calcium ions into intracellular space. Thus, intra- and intercellular biochemical cascades via activated NMDA receptors induce the hyperexcitability of thalamic VPL neurons [19–21]. The second possible speculation is that some STTs bilaterally mediate nociceptive transmissions to thalamic VPL regions via spinocervicothalamic tracts, which are decus-sated in cervical regions [22–25]. In addition, spinoreticular tracts also mediate nociceptive transmission from both sides of the spinal cord, and short-fiber multisegmental propriospinal pathways are able to bidirectionally relay the nociceptive information in the spinal cord [25, 26]. However, the contribution of dorsal column–thalamic pathway to the hyperexcitability of thalamic VPL neurons after spinal hemisection is not clear. Kim et al. [27] recently reported that a lesion of the dorsal column prevented the development of mechanical allodynia, but not the maintenance, after spinal hemisection. Based on the results of our study, we suggest that spinal hemisection produces

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**Fig. 4** Comparison of neuronal activity of thalamic VPL LT neurons following T13 spinal hemisection. a Typical waveforms of LT neurons in thalamic VPL regions from both sham-operated (top) and hemisected (bottom) rats. Background (b) and afterdischarge (d) activity did not show significant differences in both sides of VPL regions compared to sham controls, respectively. c After hemisection, brush-evoked activity shows significant difference compared to sham controls whereas pressure- and pinch-evoked activity did not show significant differences, respectively. Values are graphed as means ± SE. *P < 0.05
increased evoked activity of LT neurons in thalamic VPL regions 4 weeks after hemisection. We did not directly test the neuronal activity in the gracile nucleus following hemisection; this is a subject for future investigations. The third possible hypothesis is that a decreased concentration of monoamines contributes to thalamic VPL hyperexcitability following SCI. Monoaminergic neurons are important contributors to modulations of nociceptive transmissions in both VPL and spinal dorsal horn neurons. The final concentration of 5-HT determines physiological roles of 5-HT in the central nervous system. Eaton and Salt reported that lower concentrations of 5-HT facilitate neuronal activity, whereas higher concentrations inhibit it [28, 29]. These results indicate that decreased concentrations of monoamines (lower concentrations) via interruption by hemisection are one of factors for hyperexcitability in thalamic VPL neurons. In addition, upregulation of sodium channel expression, elevated production of chemokines, and activation of microglia in the thalamus may play important roles in the development and the maintenance of neuronal hyperexcitability in thalamic VPL regions after SCI [30, 31].

The endogenous inhibitory system, such as the GABAergic system, controls the somatosensory sensation from the spinal cord into the thalamus. However, we and others have suggested that spinal hemisection produces a loss of endogenous GABAergic tone [3, 32]. The loss of the endogenous GABAergic system may induce increased spontaneous and evoked activities following hemisection. Although our results do not show any significant change of afterdischarge activity, the spinal contusion injury animal model demonstrates significantly elevated afterdischarge activity in both spinal dorsal horn neurons and VPL neurons [28]. Taken together, the afterdischarge activity in the thalamus will be affected by the pattern and severity of the injury.

Thalamic VPL neurons receive somatosensory sensation from the spinal cord via STTs, the dorsal column lemniscal and visceral pathways [33, 34]. Anatomically, receptive field expansion and sprouting of primary afferent fiber in spinal dorsal horn neurons are common features in neuropathic states after SCI [35–37]. The altered couplings of receptive field–sensory neurons induce newly formed synaptic circuits and the excessive transmission of nociceptive information to supraspinal regions; they also cause changes in neuronal distributions. Electrophysiologically, hyperexcitable states of neurons may contribute to changes in the phenotypical property, which results in distributional changes of cell types in both the spinal dorsal horn (spinal hemisection injury) [17] and thalamic VPL (spinal contusion injury) [30]. Both animal models showed increased an incidence of WDR neurons, whereas there were fewer LT neurons. Following spinal hemisection, there was an increased incidence of thalamic VPL WDR neurons and fewer LT neurons. Taken together, we suggest that spinal hemisection injury produces similar changes in the electrophysiological property (increased spontaneous and evoked activity) and distributional changes of cell types in both the spinal dorsal horns and thalamic VPL regions.

Neuronal modulation and/or encoding ability mediate distinct perceptions of somatosensory inputs. However, once the hyperexcitable state and/or sensitization develops in thalamic VPL regions, neurons may lose the modality and/or encoding ability followed by abnormal perceptions of somatosensory inputs. Those changes produce alterations in the activation threshold, with the LT neurons becoming more sensitive in response to noxious stimuli and/or HT neurons becoming more sensitive in response to non-nocuous stimuli [38].

In conclusion, our present data demonstrate that unilateral low thoracic injury induces increases in evoked activity and results in the reorganization of neuronal distributions in bilateral thalamic VPL neurons. Thus, unilateral spinal injury produces bilateral hyperexcitability in both spinal dorsal horn neurons and thalamic VPL neurons, thereby contributing to central neuropathic pain following SCI.

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