

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

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Abstract In the present study, we have examined whether spinal hemisection injury induces changes in the electrophysiological properties of thalamic ventral posteriorlateral (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 posteriorlateral

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 posteriorlateral (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.

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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 hemisected, dorsal to ventral, at the T13 spinal cord with a micro-dissecting knife. Under an anatomical microscope, a 28-gauge needle was placed dorsal-ventrally at the midline of the cord and pulled laterally to ensure the completeness of the hemisection. The incised skin was sutured and the rats received postoperative care. Sham surgery (control group, ten rats) was performed by laminectomy of the T11–T12 spinal vertebral segments without hemisection under the same condition of anesthesia on rats of corresponding body weights. Spinal hemisection lesions included the dorsal column system, Lissauer's tract, lateral funiculus, ventral funiculus, and gray matter [13]. Experimental procedures were carried out in accordance with the guidelines of Yonsei University College of Medicine Animal Research Committee and the NIH Guide for the Care and Use of Laboratory Animals.

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 with 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 $\log(50\% \text{ threshold}) = X_f + \kappa\delta$, where X_f 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 M Ω). Based on data from previous studies, the thalamic VPL neurons were classified into three types: low threshold (LT; low threshold mechanoreceptive), high

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 \pm 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

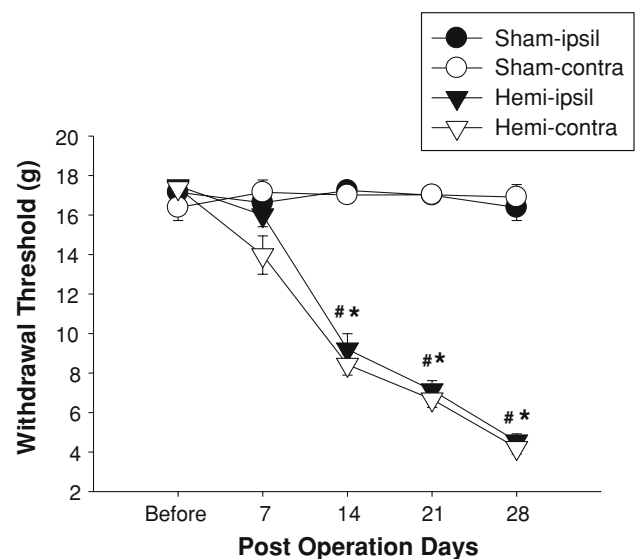


Fig. 1 Time courses of mechanical allodynic behaviors following spinal hemisection. After spinal cord injury ($n = 20$), injured (ipsilateral, *ipsil*) and uninjured (contralateral, *contra*) sides of hindpaws showed significant decreases of paw withdrawal thresholds in response to von Frey filaments 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 \pm standard error

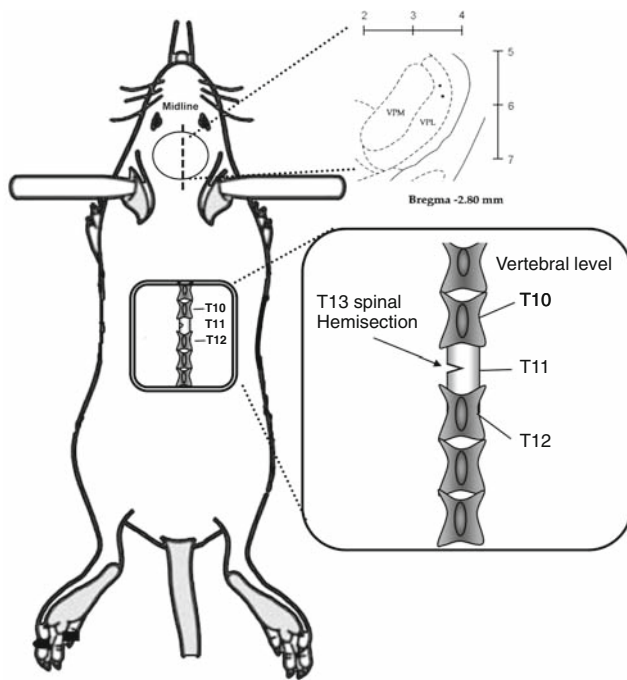


Fig. 2 The diagram of thalamic ventral posteriorlateral (VPL) neuron recording following spinal hemisection. The recording of the contralateral side (uninjured side) VPL neurons was performed by applying mechanical stimuli to the ipsilateral (injured) side of the hindpaw. In the ipsilateral (injured) side, the recording of thalamic VPL neurons was performed by applying mechanical stimuli to the contralateral side of the hindpaw. Thalamic regions were captured according to rat brain atlas (*X-axis* laterally from midline, *Y-axis* depth from surface). The closed circle (WDR, wide dynamic range) and closed square (LT, low threshold) represent the receptive field and recording site in thalamic VPL regions, respectively. VPM Ventroposterior thalamic nucleus, medial

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 ± 0.6 spikes/s. However, rats with hemisection showed significant increases in mean spontaneous activity in both ipsilateral (4.9 ± 0.7 spikes/s, $n = 19$, $P < 0.05$) and contralateral (5.0 ± 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 ± 1.3 , 14.2 ± 1.5 , and 17.4 ± 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 ± 1.6 , 24 ± 2.0 , and 26.7 ± 2.2 spikes/s, respectively) and ipsilateral (23 ± 1.6 , 21 ± 1.4

and 24.0 ± 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 ± 1.93 spikes/s. After hemisection, the mean afterdischarge activity of thalamic VPL WDR neurons in rats with hemisection was 5.68 ± 1.21 spikes/s (ipsilateral) and 7.58 ± 1.39 spikes/s (contralateral); these values were not significantly different from 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 ± 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 ± 0.7 spikes/s, $n = 10$) or contralateral (2.2 ± 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 ± 0.86 spikes/s. In comparison, in rats with hemisection, the mean activity of LT neurons was 21.9 ± 1.5 spikes/s (ipsilateral, $P < 0.05$) and 22.3 ± 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 ± 0.29 spikes/s. After hemisection, the mean afterdischarge activity of thalamic VPL LT neurons was 0.69 ± 0.26 spikes/s (ipsilateral) and 0.58 ± 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 ^a	From the midline ^b	From the surface ^c	
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

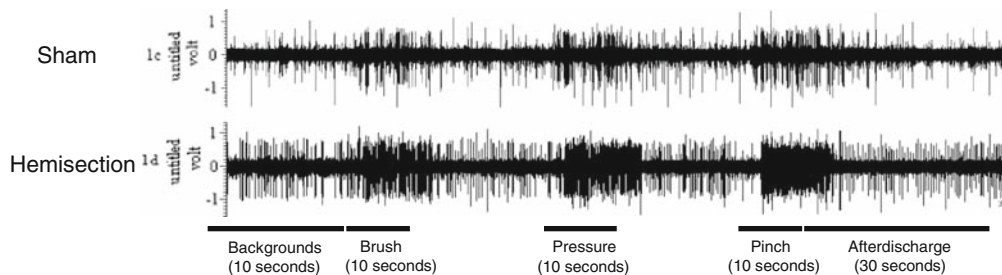
For the recording of thalamic ventral posteriorlateral (VPL) neurons, 31 neurons from sham controls were sampled and 58 neurons from hemisected rats. In sham controls, there were large populations of low threshold (LT) neurons (51.6%), whereas rats with hemisection had large populations of wide dynamic 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

^a Posteriorly from the bregma

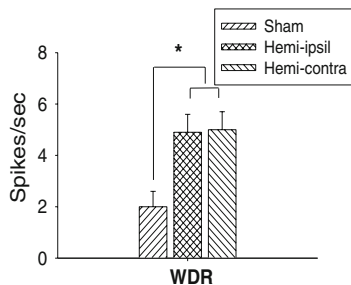
^b Laterally from the midline

^c Depth from the surface

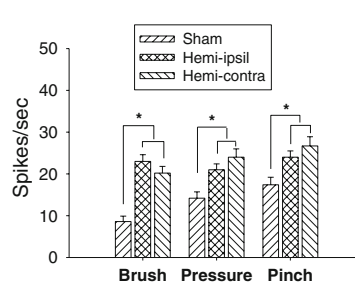
(a) Waveforms WDR neurons



(b) Background Activity



(c) Evoked activity



(d) Afterdischarge Activity

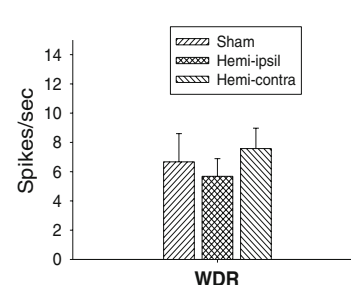


Fig. 3 Comparison of neuronal activity of thalamic VPL WDR neurons following T13 spinal hemisection. **a** Typical waveforms of WDR neurons in thalamic VPL regions from both sham (*top*) and hemisected rat (*bottom*). **b** In terms of background activity (20 s), both sides of thalamic VPL WDR neurons 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

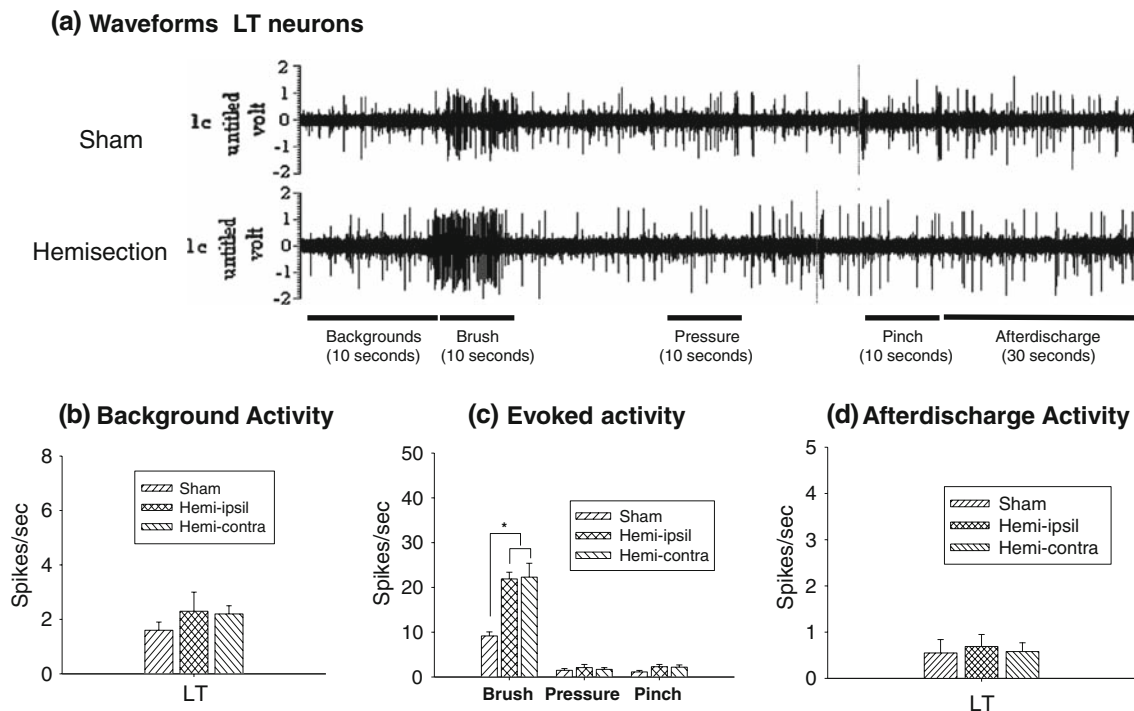


Fig. 4 Comparison of neuronal activity of thalamic VPL LT neurons following T13 spinal hemisection. **a** Typical waveforms of LT neurons in thalamic VPL regions from both sham-operated (*top*) and hemisected (*bottom*) rats. Background (**b**) and afterdischarge (**d**) activity did not show significant 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 mean \pm 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 decussated 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

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 modality 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-noxious 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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References

1. Gwak YS, Nam TS, Paik KS, Hulsebosch CE, Leem JW (2003) Attenuation of mechanical hyperalgesia following spinal cord injury by administration of antibodies to nerve growth factor in the rat. *Neurosci Lett* 336:117–120
2. Crown ED, Gwak YS, Ye Z, Johnson KM, Hulsebosch CE (2008) P38 MAP kinase inhibition attenuates central neuropathic pain following spinal cord injury in rats. *Exp Neurol* 213:257–267
3. Gwak YS, Tan HY, Nam TS, Paik KS, Hulsebosch CE, Leem JW (2006) Activation of spinal GABA receptors attenuates chronic central neuropathic pain after spinal cord injury. *J Neurotrauma* 23:1111–1124
4. Drew GM, Siddall PJ, Duggan AW (2001) Responses of spinal neurones to cutaneous and dorsal root stimuli in rats with mechanical allodynia after contusive spinal cord injury. *Brain Res* 893:59–69
5. Yeziarski RP, Park SH (1993) The mechanosensitivity of spinal sensory neurons following intraspinal injections of quisqualic acid in the rat. *Neurosci Lett* 157:115–119
6. Scheifer C, Hoheisel U, Trudrung P, Unger T, Mense S (2002) Rats with chronic spinal cord transection as a possible model for the at-level pain of paraplegic patients. *Neurosci Lett* 323: 117–120
7. Hains BC, Everhart AW, Fullwood SD, Hulsebosch CE (2002) Changes in serotonin, serotonin transporter expression and serotonin denervation supersensitivity: involvement in chronic central pain after spinal hemisection in the rat. *Exp Neurol* 175:347–362
8. Loubser PG, Donovan WH (1991) Diagnostic spinal anaesthesia in chronic spinal cord injury pain. *Paraplegia* 29:25–36

9. Hubscher CH, Johnson RD (2006) Chronic spinal cord injury induced changes in the responses of thalamic neurons. *Exp Neurol* 197:177–188
10. Finnerup NB, Sorensen L, Biering-Sorensen F, Johannesen IL, Jensen TS (2007) Segmental hypersensitivity and spinothalamic function in spinal cord injury pain. *Exp Neurol* 207:139–149
11. Gerke MB, Duggan AW, Xu L, Siddall PJ (2003) Thalamic neuronal activity in rats with mechanical allodynia following contusive spinal cord injury. *Neuroscience* 117:715–722
12. LaBuda CJ, Cutler TD, Dougherty PM, Fuchs PN (2000) Mechanical and thermal hypersensitivity develops following kainate lesion of the ventral posterior lateral thalamus in rats. *Neurosci Lett* 290:79–83
13. Gwak YS, Hains BC, Johnson KM, Hulsebosch CE (2004) Effect of age at time of spinal cord injury on behavioral outcomes in rat. *J Neurotrauma* 21:983–993
14. Dixon WJ (1980) Efficient analysis of experimental observations. *Annu Rev Pharmacol Toxicol* 20:441–462
15. Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL (1994) Quantitative assessment of tactile allodynia in the rat paw. *J Neurosci Meth* 53:55–63
16. Yen CT, Honda CN, Jones EG (1991) Electrophysiological study of spinothalamic inputs to ventrolateral and adjacent thalamic nuclei of the cat. *J Neurophysiol* 66:1033–1047
17. Hains BC, Johnson KM, Eaton MJ, Willis WD, Hulsebosch CE (2003) Serotonergic neural precursor cell grafts attenuate bilateral hyperexcitability of dorsal horn neurons after spinal hemisection in rat. *Neuroscience* 116:1097–1110
18. Gwak YS, Hulsebosch CE (2005) Upregulation of Group I metabotropic glutamate receptors in neurons and astrocytes in the dorsal horn following spinal cord injury. *Exp Neurol* 95:236–243
19. Bordi F, Quartaroli M (2000) Modulation of nociceptive transmission by NMDA/glycine site receptor in the ventroposterolateral nucleus of the thalamus. *Pain* 84:213–224
20. Kolhekar R, Murphy S, Gebhart GF (1997) Thalamic NMDA receptors modulate inflammation-produced hyperalgesia in the rat. *Pain* 71:31–40
21. Silva E, Quinones B, Freund N, Gonzalez LE, Hernandez L (2001) Extracellular glutamate, aspartate and arginine increase in the ventral posterolateral thalamic nucleus during nociceptive stimulation. *Brain Res* 923:45–49
22. Downie JW, Ferrington DG, Sorkin LS, Willis WD Jr (1998) The primate spinocervicothalamic pathway: responses of cells of the lateral cervical nucleus and spinocervical tract to innocuous and noxious stimuli. *J Neurophysiol* 59:861–885
23. Smith MV, Apkarian AV, Hodge CJ Jr (1991) Somatosensory response properties of contralaterally projecting spinothalamic and nonspinothalamic neurons in the second cervical segment of the cat. *J Neurophysiol* 66:83–102
24. Smith MV, Hodge CJ Jr (1992) Response properties of upper cervical spinothalamic neurons in cats. A possible explanation for the unusual sensory symptoms associated with upper cervical lesions in humans. *Spine* 17:S375–S382
25. Basbaum AI (1973) Conduction of the effects of noxious stimulation by short-fiber multisynaptic systems of the spinal cord in the rat. *Exp Neurol* 40:699–716
26. Chung K, Coggeshall RE (1983) Propriospinal fibers in the rat. *J Comp Neurol* 217:47–53
27. Kim J, Back SK, Yoon YW, Hong SK, Na HS (2005) Dorsal column lesion reduces mechanical allodynia in the induction, but not the maintenance, phase in spinal hemisectioned rats. *Neurosci Lett* 379:218–222
28. Eaton SA, Salt TE (1989) Modulatory effects of serotonin on excitatory amino acid responses and sensory synaptic transmission in the ventrobasal thalamus. *Neuroscience* 33:285–292
29. Eaton SA, Salt TE (1995) The role of excitatory amino acid receptors in thalamic nociception. In: Besson JM, Guilbaud G, Hollats H (eds) *Forebrain areas involved in pain processing*. Paris John Libbey Eurotext, Paris
30. Hains BC, Saab CY, Waxman SG (2005) Changes in electrophysiological properties and sodium channel Nav1.3 expression in thalamic neurons after spinal cord injury. *Brain* 128:2359–2371
31. Zhao P, Waxman SG, Hains BC (2007) Modulation of thalamic nociceptive processing after spinal cord injury through remote activation of thalamic microglia by cysteine chemokine ligand 21. *J Neurosci* 27:8893–8902
32. Rausell E, Cusick CG, Taub E, Jones EG (1992) Chronic deafferentation in monkeys differentially affects nociceptive and nonnociceptive pathways distinguished by specific calcium-binding proteins and down-regulates gamma-aminobutyric acid type A receptors at thalamic levels. *Proc Natl Acad Sci USA* 89:2571–2575
33. Willis WD, Westlund KN (1997) Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol* 14:2–31
34. Zhang HQ, Rong PJ, Zhang SP, Al-Chaer ED, Willis WD (2003) Noxious visceral inputs enhance cutaneous tactile response in rat thalamus. *Neurosci Lett* 336:109–112
35. Sherman SE, Luo L, Dostrovsky JO (1997) Altered receptive fields and sensory modalities of rat VPL thalamic neurons during spinal strychnine-induced allodynia. *J Neurophysiol* 78:2296–2308
36. Christensen MD, Hulsebosch CE (1997) Chronic central pain after spinal cord injury. *J Neurotrauma* 14:517–537
37. Ondarza AB, Ye Z, Hulsebosch CE (2003) Direct evidence of primary afferent sprouting in distant segments following spinal cord injury in the rat: colocalization of GAP-43 and CGRP. *Exp Neurol* 184:373–380
38. Shim B, Kim DW, Kim BH, Nam TS, Leem JW, Chung JM (2005) Mechanical and heat sensitization of cutaneous nociceptors in rats with experimental peripheral neuropathy. *Neuroscience* 132:193–201