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Hypersensitivity caused by suppression of descending inhibitory pathways following lumbar intrathecal injection of lidocaine in rats

Masaki Fuyuta[1], Yoshihiro Takasugi[1], Masaki Tabuchi[2], Hideaki Higashino[2] and Yoshihisa Koga[1]

Departments of [1]Anesthesiology and [2]Pharmacology, Kinki University School of Medicine, Osakasayama, Osaka, 589-8511, Japan

Abstract

Although the etiology of neural block-related transient neurological sequelae following spinal anesthesia, such as transient neurological symptoms (TNS) and less serious sensory disturbances, is still unclear, previous reports have described the facilitation of ascending nociceptive pathways as the source of complications resulting from local anesthetic toxicity, needle trauma, and patient positioning. We hypothesized that, in addition to the facilitation of ascending nociceptive pathways, the intrathecal injection of local anesthetics might interrupt descending inhibitory pathways, leading to hypersensitivity.

To test this hypothesis, changes in tail flick (TF) latency were evaluated under lidocaine blockade of descending inhibitory pathways at the thoracic spinal cord level and under lumbar intrathecal lidocaine injection in rats. Furthermore, the effects of lumbar intrathecal lidocaine injection on cerebrospinal fluid (CSF) concentrations of neurotransmitters related to nociceptive transmission were investigated.

The results revealed that thoracic intrathecal lidocaine shortened TF latency immediately after injection, while lumbar intrathecal lidocaine injection initially prolonged TF latency to the cut-off point and subsequently reduced TF latency compared to the baseline. Lumbar intrathecal lidocaine caused a significant reduction in norepinephrine concentrations in the CSF. These results indicate that the reduction of TF latency following lumbar intrathecal lidocaine injection was caused by the suppression of noradrenergic descending inhibitory pathways. We concluded that the enhanced activity of dorsal horn neurons due to the suppression of descending inhibitory pathways by intrathecal lidocaine injection is one of the possible mechanisms of transient neurological sequelae.

Key words: hypersensitivity, tail flick reflex, lidocaine, descending inhibitory pathway, C-polymodal nociceptor

Introduction

Spinal anesthesia is often followed by various block-related transient neurological sequelae such as transient neurological symptoms (TNS) and less serious sensory disturbances. Despite several postulated causes of these complications, such as specific local anesthetic toxicity, needle trauma, neural ischemia, patient positioning, muscle spasm, early mobilization, and irritation of the dorsal root ganglion, the etiology of block-related transient neurological sequelae still remains unclear.[1,2]

Nociception is a sequential process by way of ascending transmissions; signals of noxious stimuli are conducted by the primary afferent neuron from peripheral nociceptors to second-order nociceptive neurons in the dorsal horn of

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the spinal cord, and sequentially projected to neurons in the medulla, pons, midbrain, thalamus, and hypothalamus. The second-order nociceptive neurons are modulated superspinally by descending inhibitory systems. Therefore, nociceptive perception is probably increased by the enhancement of ascending impulses or by the suppression of descending inhibitory systems. Pubols et al.[3] reported that anesthetic blockade of descending inhibitory pathways at the dorsolateral funiculus (DLF) enhanced the evoked activity of dorsal horn neurons, while Jones and Gebhart[4] indicated that lidocaine injection into the ventrolateral funiculus (VLF) produced an increase in the noxious heat-evoked response of dorsal horn neurons. Previous reports described the facilitation of ascending nociceptive pathways as the cause of TNS, without considering the contribution of descending inhibitory systems. We hypothesized that an intrathecal injection of local anesthetics may interrupt descending inhibitory pathways, leading to transient neurological sequelae. To test this hypothesis in an animal model, we investigated alteration of the tail flick (TF) latency under blockade of descending inhibitory pathways at the thoracic spinal cord level and the change of TF latency after lumbar intrathecal injection of lidocaine in rats. Furthermore, we examined the effect of lumbar intrathecal lidocaine injection on neurotransmitters released in relation to nociceptive transmission in cerebrospinal fluid (CSF).

Materials and Methods

The study was approved by the animal care and use committee of the Kinki University School of Medicine. Thirty-six male Sprague-Dawley rats weighing 250 to 350 g (10-12 weeks old) were studied. Rats were bred at the Life Science Research Institute, Kinki University School of Medicine, maintained under controlled conditions (temperature: 23±0.5°C; humidity: 55%; 12/12-h light/dark cycle), and fed a commercial diet, CE-2 (Clea Japan Inc., Tokyo, Japan), with tap water *ad libitum*. Experiments were performed between 13 : 00 and 17 : 00 h under controlled conditions (temperature: 23±0.5°C).

Animal Preparation

Local anesthetics were administered through a thoracic or lumbar intrathecal catheter in experiments 1 and 2. The subarachnoid space was cannulated with a Teflon-lined polyethylene tube (0.3-mm O.D. and 0.11-mm I.D.; Microspinal Catheter, Hakko Co., Ltd., Nagano, Japan) by application of the modified method of Sakura et al.[5] and Jensen and Yaksh.[6] In brief, rats were anesthetized by inhalation of 2% isoflurane in oxygen using a mask. The catheters were passed through an incision in the atlanto-occipital membrane and extended 3 cm to the level of the mid-thoracic cord or 11 cm to a level caudal to the conus medullaris. The other end of the catheter was fixed in the subcutaneous tissue to avoid catheter displacement. The catheter was filled with normal saline, and the end was heat-sealed. One week later, rats that exhibited any evidence of sensory or motor dysfunction were excluded from the study. In the preliminary experiments, we investigated the doses to produce motor paralysis and anesthesia in the forelimbs or hindlimbs by thoracic or lumbar intrathecal injection of 2% lidocaine containing indigo carmine (1 : 1), respectively. Thoracic intrathecal injection of 10 μl of solution produced the signs in the forelimbs, and the dye remained the upper thoracic spinal cord (C1-Th2). Lumbar intrathecal injection of 20 μl of solution produced the signs in the hindlimbs, and the dye distributed from Th12 to the caudal spinal cord. Therefore, 10 μl and 20 μl of 1% lidocaine were applied to the thoracic and lumbar intrathecal injection in the experiment 1-3.

Upon completion of the experimental series, 3 each of the thoracic and lumbar intrathecal catheterized animals were sacrificed by intraperitoneal injection of an overdose of pentobarbital after intrathecal infusion of 10 or 20 μl of indigo carmine, respectively. The location of the catheter tip and distribution of dye in the subarachnoid space were ascertained by of vertebral bone removal.

Experiment 1: Alteration of Tail Flick Latency After Thoracic Intrathecal Lidocaine Injection

To demonstrate the shortening of TF latency, representing an increase in the noxious heat-evoked response under lidocaine blockade at the thoracic spinal cord level, 12 rats that were implanted with thoracic intrathecal catheters were randomly divided into 2 groups of 6 rats each, the normal saline and lidocaine groups.

The Tail-Flick Unit (Model 7360, Ugo Basile, Varese, Italy) was utilized, and TF latency was measured using the method described by Ta-

kasugi et al.[7] A heat intensity setting of IR20 and inhalation of 1% isoflurane in oxygen was used for TF testing. The ventral aspect of the distal 5 to 6 cm of the tail was exposed to radiant heat. A 10-s cut-off was used to minimize the risk of tissue damage. Rats were placed in a plastic box (22×6.5×6.5 cm) that had 2 holes in the anterior wall for gas inlets and sampling, and 1 hole in the posterior wall through which the tail protruded. The concentrations of isoflurane and oxygen in the box were continuously measured using an anesthetic gas analyzer (Capnomac Ultima, Datex, Helsinki, Finland). The mean of the latter 5 TF latencies of 7 consecutive measurements with a 10-s time interval was used as the representative value.

Prior to each experiment, the rats were placed in the boxes and exposed to the mixed gas for 20 min, and baseline TF latencies were measured. Rats of the normal saline and lidocaine groups received an intrathecal injection of 10 μl of normal saline or 1% lidocaine, respectively, followed by another injection of 5 μl of normal saline in both groups with a Hamilton microsyringe. Following the intrathecal injection of drugs, each subject was tested at 10-min intervals for 60 min.

The TF latency was converted to represent the maximum possible effect (MPE) according to the following formula:

%MPE=[(test latency)−(baseline latency)/(cut-off time)−(baseline latency)]×100

Experiment 2: Alteration of Tail Flick Latency after Lumbar Intrathecal Lidocaine Injection

Twelve rats that were implanted with lumbar intrathecal catheters were randomly divided into 2 groups of 6 rats each, the normal saline and lidocaine groups. TF tests were performed using the same protocol as in experiment 1 following lumbar intrathecal injection of 20 μl of normal saline or 1% lidocaine, respectively. Each subject was tested at 10-min intervals for 60 min following the intrathecal injection of drugs. The TF latency was evaluated as the %MPE.

Experiment 3: Alteration of Neurotransmitter Concentrations in CSF After Lumbar Intrathecal Lidocaine Injection

Twelve rats with lumbar intrathecal catheters were randomly divided into 2 groups of 6 rats each. The rats were exposed to 1% isoflurane in oxygen from 20 min prior to the lumbar intrathecal injection of drugs until completion of the experiment. A 30-gauge needle attached to a Hamilton microsyringe was introduced between L5 and L6 intervertebral spaces. The needle tip was advanced into the lumbar subarachnoid space and its position confirmed by observation of the tail flick. Next, 20 μl of normal saline or 1% lidocaine was injected. Thirty min later, 70 to 100 μl of CSF was aspirated from the cisterna magna by application of the method of Takasugi et al..[8] All CSF samples, except 1 sample from the normal saline group that was contaminated with blood, were quick-frozen in liquid nitrogen and stored at −80°C until assays. Concentrations of amino acids and monoamines in the CSF samples were determined by an isocratic high-performance liquid chromatographic (HPLC) method and by a gradient reversed-phase HPLC method, respectively, with a coulometric array electrochemical detector (Model 5600A CoulArray® System, ESA Inc., Chelmsford, MA, USA). The chromatographs were quantitatively analyzed by CoulArray® for Windows Data Processing Module Ver. 1.04 (ESA Inc.). CSF samples were analyzed for the levels of glutamate (Glu), γ-aminobutyric acid (GABA), norepinephrine (NE), 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), serotonin (5-HT) ,and 5-hydroxyindoleacetic acid (5-HIAA).

Statistical Analysis

Data are expressed as the mean±standard deviation. TF latency changes over time were compared using repeated measures ANOVA and comparisons among groups were analyzed by ANOVA followed by post-hoc Dunnett's or Tukey's multiple comparison test as indicated. Differences among groups regardings amino acids or monoamine concentrations were determined using an unpaired t-test. Statistical analysis was performed using Prism 5 for Windows Ver. 5.01 (GraphPad Software Inc., San Diego, CA, USA). The significance level was set at $P<0.05$.

Results

Location of Intrathecal Catheter Tip and Distribution of Dye

In rats with thoracic intrathecal catheters, the catheter tips were located between C4 and C5, and indigo carmine dye extended in the subarachnoid space between C1 and Th2. In rats with lumbar intrathecal catheters, the tips of the cath-

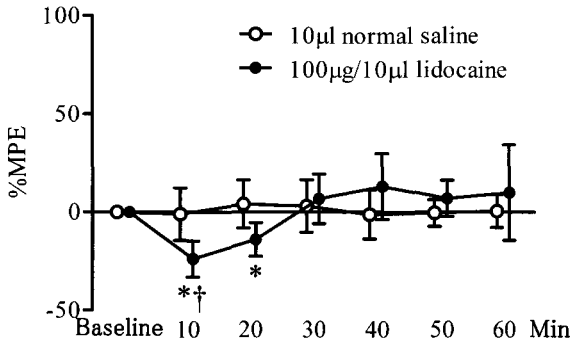

Fig. 1 Changes in tail flick latency (%MPE) following thoracic intrathecal injection of 10 μl of normal saline or 1% lidocaine. The time-course of tail flick latencies in the normal saline group did not change during the study period. Tail flick latencies were significantly shortened at 10 and 20 min after thoracic intrathecal lidocaine injection (Dunnett's multiple comparison test). Open circles denote the normal saline group, and closed circles the lidocaine group. Data are expressed as the mean ± standard deviation. *: $P<0.05$ vs. baseline; †: $P<0.05$ vs. normal saline group.

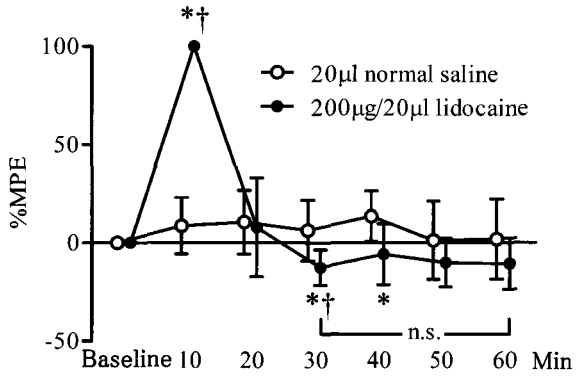

Fig. 2 Changes in tail flick latency (%MPE) following lumbar intrathecal injection of 20 μl of normal saline or 1% lidocaine. The time-course of tail flick latencies in the normal saline group did not change during the study period. In the lidocaine group, tail flick latencies were extended to the cut-off time (10 s) immediately after injection, and then significantly shortened at 30 min after lumbar intrathecal injection (Dunnett's multiple comparison test). The reduction of TF latency continued to the end of the session (Tukey's multiple comparison test). Open circles denote the normal saline group, and closed circles the lidocaine group. Data are expressed as the mean ± standard deviation. *: $P<0.05$ vs. baseline; †: $P<0.05$ vs. normal saline group; n.s.: not significant.

eters were located between L3 and L4, and indigo carmine dye extended in the subarachnoid space between Th12 and the apex of the conus medullaris.

Experiment 1: Alteration of Tail Flick Latency After Thoracic Intrathecal Lidocaine Injection

There was no significant difference in baseline TF latencies between the normal saline and lidocaine groups, these being 4.6±0.4 s (estimated skin temperature of 47.7±3.3°C[7] and 4.9±0.5 s (48.5±4.1°C) respectively. Assessment of the time-course of changes in TF latencies (%MPE) in the normal saline group showed no variation, whereas those in the lidocaine group significantly decreased 10 min after injection as compared to the baseline (−24.6±9.2%, $P<0.05$). TF latencies in the lidocaine group at 10 and 20 min were significantly lower than those in the normal saline group ($P=0.005$, 0.024) (Fig. 1).

After completion of the experiment, 10 μl of 1% lidocaine was injected intrathecally, with all rats revealing motor and sensory paralysis in the upper limbs with intact nociceptive reflexes in the lower limbs and tail.

Experiment 2: Alteration of Tail Flick Latency After Lumbar Intrathecal Lidocaine Injection

There was no significant difference in baseline TF latencies between normal saline and lidocaine groups, their values being 4.7±0.5 s (46.3±4.1°C) and 4.5±0.5 s (47.7±4.1°C), respectively. The time-course of %MPE in the normal saline group did not change over the study period. In the lidocaine group, TF latency at 10 min after injection was prolonged to the cut-off time, decreasing significantly compared to the baseline at 30 min after injection (−12.6±9.0%, $P<0.05$). The reduction of TF latency continued until the end of the session (Fig. 2). Although TF latency at 60 min after injection in all rats was not significantly different compared with the baseline, values in 5 of 6 rats decreased compared with the baseline (−14.7±8.9%). At 30 and 40 min after injection, TF latencies in the lidocaine group were significantly lower than those in the normal saline group ($P<0.05$).

After the completion of the experiment, 20 μl of 1% lidocaine was injected intrathecally, and all rats revealed motor and sensory paralysis in the lower limbs and tail.

Experiment 3: Alteration of Neurotransmitter Concentrations in CSF after Lumbar Intrathecal Lidocaine Injection

There was no difference between groups in the CSF concentrations of Glu and GABA 30 min after lumbar intrathecal injection of lidocaine

(Fig. 3). CSF concentrations of NE in the lidocaine group were significantly lower than those in the normal saline group (0.22±0.04 ng/ml and 0.35±0.07 ng/ml, respectively, $P<0.05$), although CSF concentrations of MHPG, 5-HT, and 5HIAA were not significantly different between the groups (Fig. 4).

Discussion

This study revealed that thoracic intrathecal lidocaine shortened the TF latency immediately after injection, while lumbar intrathecal lidocaine resulted in an initial prolongation of TF latency to the cut-off time followed by its subsequent reduction compared to the baseline. Lumbar intrathecal lidocaine caused a reduction of the NE concentration in the CSF.

Transient neurological sequelae following spinal anesthesia are not uncommon; the reported incidence of TNS widely varies from 4-33% in prospective randomized studies after lidocaine spinal anesthesia,[9] and that of less serious sensory disturbances is reportedly as high as 27.8% after single-shot spinal anesthesia and 49.6% after continuous spinal anesthesia.[2] The painful symptoms of TNS, originating in the buttocks and radiating to the lower extremities, commence within 24 h after complete recovery from spinal anesthesia, and disappear by the 10th postoperative day without any residual neurological symptoms.[10] Increased Glu concentrations in the CSF and vacuolation of the dorsal funiculus following intrathecal injection of high-dose lidocaine in animal models are postulated as possible sources of neurotoxicity.[11-13] In contrast, Freedman et al.[14] reported that injection concentrations ranging from 1.5-5% conferred a similar risk of TNS. While Puolakka et al.[2] postulated that neural and/or vascular compression during surgery may be a major factor in minor neurological sequelae such as numbness

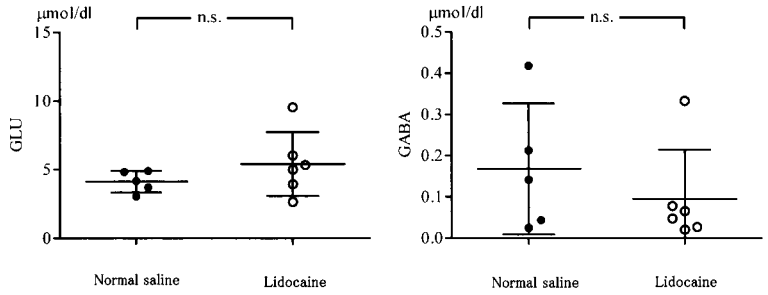

Fig. 3 Comparison of glutamate and GABA levels in cerebrospinal fluid following lumbar intrathecal injection of 20 μl of normal saline or 1% lidocaine. There were no significant differences in glutamate and GABA levels between the normal saline and lidocaine groups 30 min after injection. Data are expressed as the mean ± standard deviation. GLU: glutamate, n.s.: not significant.

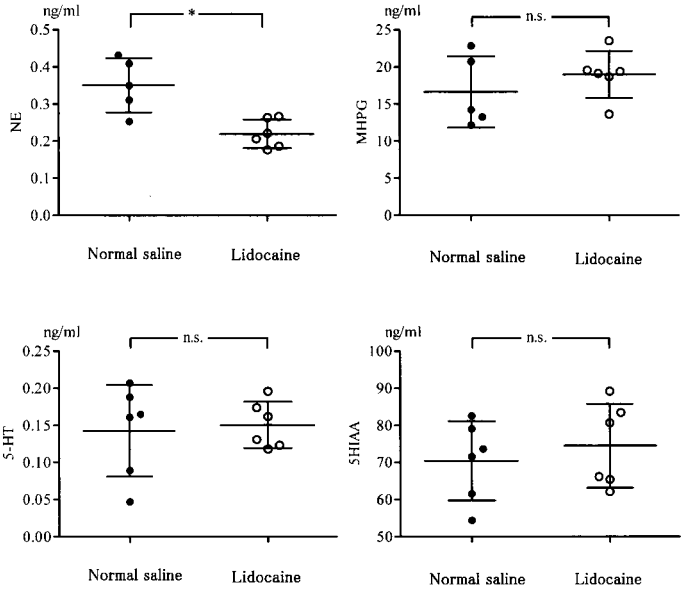

Fig. 4 Comparison of norepinephrine (NE), 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) levels in cerebrospinal fluid following lumbar intrathecal injection of 20 μl of normal saline or 1% lidocaine. There was a significant difference in NE levels between normal saline and lidocaine groups 30 min after injection, whereas no significant differences were noted in MHPG, 5-HT and 5HIAA levels between groups. Data are expressed as the mean ± standard deviation. *: $P<0.05$ between groups; n.s.: not significant.

and dysesthesia, the etiology of sensory disturbances is still unclear.

Thermosensitive ion channels that are expressed in primary sensory neurons belong to the transient receptor potential (TRP) superfamily, including TRPV1, TRPV2, TRPV3, TRPV4, TRPM8, and TRPA1. Aδ fibers exhibit TRPV2-containing channels (>52°C of the thermal activation threshold) but do not express TRPV1 (>43°C), while C fibers exclusively exhibit TRPV1.[15,16] The TRPV1-positive neurons mediate thermal hyperalgesia or tactile allodynia.[17] Takasugi et al.[7] reported that a radiant heat intensity of 161.5 mW/cm^2 results in a skin temperature of 65°C after 10 s of radiation, and stimulates C-polymodal nociceptors, while 1% isoflurane inhalation excludes the influence of supraspinal structures and provides reliable TF latencies on repeated TF testing. We applied this setting of TF testing in this study, and confirmed thermal hypersensitivity immediately after thoracic subarachnoidal lidocaine injection and subsequent to anesthesia with lumbar subarachnoidal lidocaine injection.

The afferent input to dorsal horn neurons is inhibited by descending pathways, both pre- and postsynaptic, suggesting that lesions of descending pathways should lead to an immediate facilitation of afferent transmission. Patients with spinal cord injuries develop hyperexcitability, expressed as hypersensitivity to pain below the level of the lesion, due to a lack of descending inhibition,[18–20] and disruption of descending antinociceptive tracts in clip-compression models of spinal cord injury, producing tactile allodynia and hyperalgesia caudal to the injury.[21]

Chronic spinal cord injury, such as spinal cord transection, decerebration,[6] and anesthetic[3] or cold blockade[22] of the spinal cord, has been used as a means to interfere with descending transmission in animals. Compared with lesions and cold blockade, lidocaine blockade of the spinal cord has the advantages of being reversible, causes less damage to the cord, preserves of the blood-spinal cord barrier and facilitates the determination of the extent of anesthetic diffusion by the addition of a dye to the drug. However, it also has disadvantages such as a variable onset and relatively short duration of its peak effect with a single dose.[3]

Janss and Gebhart[22] reported that bilateral lidocaine blockade of the DLF significantly shortened TF latencies, while blockade of the VLF increased the noxious heat-evoked response of dorsal horn neurons. Pubols et al.[3] studied electrophysiologically and reported that lidocaine blockade of descending inhibitory pathways at the DLF enhanced evoked activity of dorsal horn neurons. Furthermore, they assumed that the heat-evoked discharges of multireceptive cells in the dorsal horn, which were increased by lidocaine blockade of the DLF, were primarily due to the effects on input from C- rather than Aδ-heat-sensitive nociceptors. Therefore, it seems highly probable that the shortening of TF latencies on cutaneous afferent input mediated by C-polymodal nociceptors following lidocaine blockade of the thoracic spinal cord was due to the suppression of descending inhibitory pathways, and that the suppression was more prolonged compared to the inhibition of ascending nociceptive pathways by lumbar intrathecal lidocaine injection.

5-HT and NE, which are released from serotonergic or noradrenergic descending neurons, bind to presynaptic 5-HT or α_{2A} receptors in the dorsal horn, and modulate excitatory synaptic transmission. Furthermore, the activation of both supraspinal and spinal α_1-adrenoceptors evokes pronociceptive effects via noradrenergic descending spinal pathways.[23–24] Excitatory synaptic transmission between primary afferent neurons and second-order nociceptive neurons is mediated by neurotransmitters, i.e., Glu from Aδ-fibers, and Glu, substance P, and calcitonin gene-related peptide (CGRP) from C-fibers. The suppression of descending pathways consequently produces both a decrease in 5-HT and NE release from the descending inhibitory neurons, and inhibits the activation of both 5-HT and α_{2A} receptors in the dorsal horn, followed by an increase in neurotransmitter release from primary afferent neurons. In this study, lumbar intrathecal lidocaine injection led to a decreased level of NE and an unchanged level of Glu and 5-HT in the CSF. Gebhart and Ossipov[25] indicated that inhibition of the spinal nociceptive TF reflex is mediated by spinal α_2-adrenoceptors. Hence, our results indicate that the subsequent reduction of TF latency after prolongation by lumbar intrathecal lidocaine injection is dominantly caused by the suppression of noradrenergic descending inhibitory pathways mediated by spinal α_2-adrenoceptors, even though a decrease in NE release may possibly

produce an antinociceptive effect mediated by α_1-adrenoceptors. The presynaptic inhibition of Glu release from primary afferent neurons onto lamina II neurons likely plays an important role in the analgesic action produced by activation of the descending noradrenergic system.[26] Anesthetic interference of the sodium channels of primary afferent neurons inhibits the conduction of ascending nociceptive impulses, and suppresses excitatory neurotransmitter release at the dorsal horn. Therefore, a decrease in excitatory neurotransmitter release due to the suppression of ascending nociceptive conduction and an increase of neurotransmitter release caused by the suppression of descending inhibitory pathways may be simultaneously produced in primary afferent neurons with lumbar intrathecal lidocaine injection. Although we did not measure the concentrations of substance P and CGRP in the CSF, counteractive neurotransmitter release in the dorsal horn may be one of the possible causes of unchanged Glu levels in the CSF following lumbar intrathecal lidocaine injection.

Spinal anesthesia-related neurological sequelae vary from minor sensory disturbances to transient but intensely painful symptoms. Recent findings have demonstrated that nerve membrane damage is induced by highly concentrated local anesthetics.[27] Intrathecal injection of high concentrations of local anesthetics such as 10 and 20% lidocaine and 5% bupivacaine result in the development of histological damage including axonal degeneration, vacuolation of the dorsal funiculus,[12,13] and increased concentrations of Glu in the CSF of animals.[28] Since high concentrations of Glu are known to be neurotoxic, the neurotoxicity of high concentrations of local anesthetics may possibly be related to Glu neurotoxicity,[28] although intrathecal injections of a solution containing lower concentrations of lidocaine have also been reported to cause TNS.[14,29] We demonstrated the further prolongation of the suppression of descending inhibitory pathways than inhibition of ascending nociceptive pathways following lumbar intrathecal injection of lower concentrations of lidocaine. Although we did not investigate the effect of intrathecal injection of a high concentration of lidocaine, we can speculate that it causes prolonged and severe neurotoxicity due to the intense suppression of descending inhibitory pathways following increased Glu levels in the CSF.

Thus, the results of this study suggest that drugs activating descending inhibitory systems, such as tricyclic antidepressants and morphine, would probably be useful in treating serious neurological sequelae resulting from neurological blockade following intrathecal local anesthetic injection. The complete elucidation of the effects of intrathecal local anesthetics on the descending inhibitory system and the release of neurotransmitters and spinal cord degeneration requires further investigation.

This review was partially presented at the 54th Annual Meeting of the JSA(Japanese Society of Anesthesiologists) in May and June 2007, in Sapporo, Japan.

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