Position of Spinothalamic Tract Axons in Upper Cervical Spinal Cord of Monkeys

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Zhang, Xijing, Christopher N. Honda, and Glenn J. Giesler, Jr. Position of spinothalamic tract axons in upper cervical spinal cord of monkeys. J Neurophysiol 84: 1180–1185, 2000. Percutaneous upper cervical cordotomy continues to be performed on patients suffering from several types of severe chronic pain. It is believed that the operation is effective because it cuts the spinothalamic tract (STT), a primary pathway carrying nociceptive information from the spinal cord to the brain in humans. In recent years, there has been controversy regarding the location of STT axons within the spinal cord. The aim of this study was to determine the locations of STT axons within the spinal cord white matter of C2 segment in monkeys using methods of antidromic activation. Twenty lumbar STT cells were isolated. Eleven were classified as wide dynamic range neurons, six as high-threshold cells, and three as low-threshold cells. Eleven STT neurons were recorded in the deep dorsal horn and nine in superficial dorsal horn. The axons of the examined neurons were located at antidromic low-threshold points (<30 μA) within the contralateral lateral funiculus of C2. All low-threshold points were located ventral to the denticulate ligament, within the lateral half of the ventral lateral funiculus (VLF). None were found in the dorsal half of the lateral funiculus. The present findings support our previous suggestion that STT axons migrate ventrally as they ascend the length of the spinal cord. Also, the present findings indicate that surgical cordotomies that interrupt the VLF in C2 likely disrupt the entire lumbar STT.

INTRODUCTION

Anterolateral cordotomy has been used to treat chronic pain since the early years of the last century (Spiller and Martin 1912). It is believed that this lesion produces analgesia in part because it interrupts the spinothalamic tract (STT), which is generally thought to be the principal pathway that carries nociceptive information from the spinal cord to the forebrain (reviewed in Albe-Fessard et al. 1985; Willis 1985). Although the organization of STT axons in the spinal cord of primates and humans has been investigated many times with a variety of techniques, uncertainties remain. For example, in virtually all studies in which axonal degeneration methods were used, it was found that ascending STT axons were located entirely within the ventral half of the spinal cord white matter (Bowsher 1961; Kerr and Lippman 1974; Mehler et al. 1960; Mott 1895). However, several more recent anatomic studies have indicated that STT axons are not restricted to the ventral half of the cord. Apkarian and Hodge (1989) found that STT axons originating from neurons in the superficial dorsal horn (SDH) of monkeys ascend in the dorsal lateral funiculus (DLF). In addition, Craig (1991, 2000) reported that injections of Phaseolus vulgaris leucoagglutinin (PHA-L) into the superficial dorsal horn labeled ascending axons in both the DLF and ventral lateral funiculus (VLF). Many were concentrated at the level of the denticulate ligament. Also, Ralston and Ralston (1992) found that small lesions in the lateral funiculus centered at the level of the denticulate ligament blocked the anterograde labeling of STT axons in the thalamus. Taken together, these findings indicate that STT axons are more widely scattered within the lateral funiculus than was originally believed.

Recently, we have re-examined the organization of primate STT axons within the thoracic spinal cord and cervical enlargement using methods of anterograde labeling (Zhang et al. 2000). These methods have several important advantages over anatomical methods for determining the locations of STT axons (see Zhang et al. 2000). For example, unlike anterograde tracing methods, individual STT axons can be unambiguously identified and located at multiple levels of spinal cord. In addition, the response characteristics of the examined axons can be determined. We found that in mid-thoracic segments the axons of STT neurons in the marginal zone are frequently located within the DLF, at a level near that of the denticulate ligament. In contrast, the axons of STT neurons in the deep dorsal horn (DDH) were found substantially deeper, most often within the VLF (Zhang et al. 2000). As the axons reached the level of the cervical enlargement, the STT had shifted ventrally. At this level, although the axons of neurons in the SDH continued to be located dorsal to those of DDH neurons, both groups of STT axons were found within the VLF. No STT axons were located within the DLF. This finding appeared to conflict with a large number of early clinical and anatomical studies (Hyndman and Van Epps 1939; Kahn and Rand 1952; Walker 1940; White 1954), in which the conclusion was reached that lumbosacral STT axons migrate dorsally as they ascend the length of the spinal cord. These workers suggested that STT axons assume a position at, or slightly dorsal to, the denticulate ligament in the rostral spinal cord.

We have used the methods of anterograde activation to examine the organization of STT within the upper cervical segments in monkeys. We have done so for two reasons. First, we wished to test the hypothesis that STT axons shift ventrally as they ascend through rostral segments and are located entirely

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within the VLF in the rostral cord. Second, additional accurate information on the location of STT axons at this level would be of value since cordotomies continue to be frequently carried out in the rostral cervical cord (Garcia-Larrea et al. 1993; Jackson et al. 1999; Krol and Arbit 1993; Lahuerta et al. 1994; Mullan et al. 1963; Nagaro et al. 1993, 1994; Orlandini 1995; Sanders and Zurmond 1995).

METHODS

All procedures followed the guidelines of the International Association for the Study Pain and were approved by the Institutional Animal Care and Use Committee. The methods used in this study were described in detail recently (Zhang et al. 2000). Briefly, six female monkeys (Macaca fascicularis or mulatta) weighing 3.4 – 6.4 kg were anesthetized initially with ketamine (100 mg/kg im), followed by α-chloralose (60 mg/kg iv), and maintained with a continuous infusion of nembutal (2–4 mg · kg⁻¹ · h⁻¹ iv). Animals were placed in a stereotaxic frame, paralyzed with Flaxedil, and artificially ventilated. Body temperature, end-tidal CO₂, and blood pressure were monitored and kept within physiological limits. Laminectomies were made over lumbar and upper cervical segments. Craniotomies were made over the thalamus. The search stimulus consisted of cathodal current pulses (200 μA, 500 μA) delivered within contralateral ventral posterior lateral nucleus (VPL) through a stainless steel electrode. Single-unit recordings were made in the lumbar enlargement using tungsten microelectrodes (5 MΩ). After isolating an antidromically identified unit, the stimulating electrode in the thalamus was moved dorsally and mediolaterally until a point was located at which the antidromic threshold was ≤ 30 μA. Only cells with a low-threshold point in the thalamus were studied, and all units included in this study met the criteria for antidromic activation (see Fig. 3, a1–a3). Cutaneous receptive fields and response characteristics of examined neurons were determined using innocuous and noxious mechanical stimulation. Responses to cutaneous stimuli were used to classify the examined neurons as low-threshold (LT), wide-dynamic range (WDR), or high-threshold (HT) cells (see Dado et al. 1994 for details).

Once antidromic activation from the contralateral thalamus was demonstrated, a second stainless steel stimulating electrode was inserted into the lateral funiculus of C2 contralateral to the recording site. Initially, large current pulses (500 μA, 200 μs) were delivered as the electrode was lowered through the cord until the same neuron was antidromically activated. The threshold for antidromic activation was then determined at 200 – 400 μs intervals in each track. The electrode was lowered through a series of tracks, each separated by 500 μm, across the medial-lateral extent of the cord. At the lowest threshold point for antidromic activation, each neuron was activated using current pulses ≤ 30 μA. In each case, action potentials at the lowest threshold point in the cord collided with antidromic action potentials produced at the lowest threshold point in the thalamus, establishing that action potentials elicited at both stimulation sites traveled in the same axon.

Because the location of more than one STT axon was examined on each side of the cord in the same monkey, efforts were made to preserve the integrity of STT axons that were yet to be examined. In these cases, electrolytic lesions were made 1.5 mm medial to the low-threshold points at the same anterior-posterior plane (see Zhang et al. 2000 for details of the methods used to reconstruct the location of these low-threshold points). Lesions were made directly at each low-threshold point for the final case examined on each side of the cord. Electrolytic lesions were also made at each recording site and low-threshold point in the thalamus.

Monkeys were perfused with 0.9% saline followed by 10% formalin containing 1% potassium ferrocyanide (Prussian blue reaction). The areas of the thalamus and spinal cord containing lesions were cut transversely at 100 and 50 μm using a freezing microtome. Sections were counterstained with neutral red and microscopically examined. The locations of lesions were reconstructed with the aid of an attached camera lucida drawing tube.

RESULTS

Twenty neurons in the lumbar enlargement were antidromically activated from low-threshold points (≤ 30 μA) in the contralateral thalamus. Most low-threshold points were concentrated in the ventral and lateral parts of VPL (Fig. 1A). One low-threshold point was located in the posterior thalamus, within the suprageniculate nucleus (Fig. 1B).

The locations of lesions marking 20 recording sites are shown in Fig. 2. Two units were recorded in L5, nine in L6, and nine in L7. Nine recording sites were located in the SDH and 11 in the DDH. Six STT neurons were classified as HT neurons, 11 as WDR neurons, and 3 as LT neurons. Five HT neurons were recorded in the SDH, one in DDH. Four WDR neurons were recorded in the SDH, seven in DDH. All LT neurons were recorded in DDH.

Nineteen STT neurons had excitatory receptive fields re-
Strikingly, activating STT neurons was 13.3 mean current threshold at the lowest threshold point for antidromic activation in the contralateral lateral funiculus in C2 segment. The neuron had a receptive field on the ipsilateral foot and leg (Fig. 3D). It responded to innocuous mechanical stimuli but responded at higher frequencies to noxious mechanical stimuli and was classified as a WDR neuron (Fig. 3E).

The locations of 20 low-threshold points in the white matter of C2 are illustrated in Fig. 4. All low-threshold points were located in the medial-lateral center or lateral half of the VLF. There were no significant differences in the distance from the lateral edge of the cord for SDH versus DDH neurons (Fig. 4A) nor between the three physiological classes of neurons (Fig. 4B). In contrast to our previous results in thoracic segments and in the cervical enlargement (Zhang et al. 2000), within C2, there was no statistically significant difference between the dorsal-ventral position of the axons of SDH neurons and DDH neurons (P > 0.08, t-test).

Figure 4B illustrates the locations of six low-threshold points for activation of axons of HT neurons (5 SDH neurons, 1 DDH neuron), 11 for activation of axons of WDR neurons (4 SDH neurons, 7 DDH neurons), and three for LT neurons (3 DDH neurons). The low-threshold points for activation of HT and WDR neurons were located throughout the VLF. The low-threshold points for activation of LT neurons were significantly ventral to those of HT (P ≤ 0.001) and WDR neurons (P ≤ 0.002).

**DISCUSSION**

Spiller and Martin (1912) performed the first surgical interruption of the VLF to treat intractable pain in a patient with a tumor in the lumbosacral spinal cord. To gain access to the cord, an open laminectomy was performed over thoracic vertebrae. The new method proved to be highly effective and it became widely used to treat a variety of types of pain originating in lower thoracic and lumbosacral dermatomes. It was believed that at that time that sectioning of the upper cervical cord would produce severe side effects (e.g., “softening” of the medulla, Stookey 1931). As a result, for almost two decades following the initial description of cordotomies, they were not performed in patients who had pain originating in upper thoracic and cervical dermatomes. However, in 1931, Stookey exposed upper cervical segments with an open laminectomy and sectioned the VLF bilaterally in two patients suffering from carcinoma of the breast. The technique blocked the pain in the patients and did not produce the feared side effects. As a result, the method of open upper cervical cordotomy became a widely used treatment for severe pain (Foerster and Gagel 1932; French 1974; Kahn and Rand 1952; Peet et al. 1933; Roulhac 1953; Schwartz 1960; White 1954). Mullan et al. (1963) introduced an improvement in upper cervical cordotomies in which the VLF was severed without producing the surgical trauma of an open laminectomy. A radioactive needle composed of strontium-yttrium was inserted percutaneously between C1 and C2 vertebrae and placed on the exterior surface of the dura adjacent to the VLF. The size of the lesion was controlled by varying the proximity of the needle to the
cord or the duration of exposure of the cord to the radiation. In 1965, this method was improved by using radiofrequency electric currents instead of radiation to produce the lesion (Rosomoff et al. 1965). In recent years, the number of cordotomies that are performed has decreased, primarily as a result of improvements in pharmacologic and other treatments of pain. However, upper cervical cordotomy continues to be used frequently to treat intractable pain (Garcia-Larrea et al. 1993; Jackson et al. 1999; Lahuerta et al. 1994; Nagaro et al. 1993, 1994; Orlandini 1995, Sanders and Zurmond 1995). Indeed, these recent papers describe the results of upper cervical cordotomies in several hundred patients. One of the goals of the

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**FIG. 3.** An example of an STT neuron recorded in the DDH with an axon that ascended in contralateral ventral lateral funiculus (VLF) of C2. A: the lowest threshold point in contralateral ventral posterior lateral nucleus (VPL) for antidromically activating the neuron. The antidromic response had a stable latency (3 overlapping traces in a1), followed high-frequency trains of pulses (a2), and collided with orthodromic action potentials (a3). Amplitude and timing of stimulus pulses are indicated below digitized oscillographic traces. B: this STT neuron was also antidromically activated in contralateral C2 (b1). Spikes elicited from both low-threshold points in the spinal cord collided with those elicited in VPL (b2–b3). Interstimulus intervals: b2 = 1.6 ms; b3 = 1.5 ms. A second neuron was antidromically activated (small spikes in records) from the VLF at a longer latency. Arrows in a3 and b3 indicate time at which antidromic spikes would have occurred had they not collided. C: recording site; D: receptive field; E: histograms of the responses to innocuous and noxious mechanical stimuli applied to cutaneous receptive field. The mean firing frequency during each stimulus is listed within parentheses.
The present study was to provide more precise information on the location of STT axons as they ascend through the rostral cervical cord, information that would be of value to surgeons attempting to transect them.

In a previous study (Zhang et al. 2000), it was found that in mid-thoracic segments, the axons of STT neurons in the SDH were frequently located within the DLF, near the level of the denticulate ligament. The axons of neurons in the DDH were frequently located within the VLF. In the cervical enlargement, STT axons from the SDH continued in a position dorsal to those of DDH neurons, although the axons from both areas had shifted into the VLF (Zhang et al. 2000). At each of the examined levels, SDH neurons were found to be statistically significantly dorsal to those of DDH neurons. In the present study, no significant difference was found in the dorsal-ventral position of low-threshold points for SDH and DDH neurons in C2. Therefore, we conclude that the axons of SDH and DDH neurons are not segregated in C2. However, this conclusion is made tentatively since 7 of the most dorsal 11 low-threshold points in the VLF were those of SDH neurons and seven of the most ventral nine low-threshold points were those of DDH neurons. Our conclusion that the axons of STT neurons in the SDH and DDH are not segregated within C2 is in agreement with the results of recent studies by Craig (1991, 2000). He examined the distribution within the spinal cord white matter of ascending lamina I axons in the spinal cord white matter of cats and monkeys. Injections of PHA-L into the SDH of the lumbar and cervical enlargements labeled a number of ascending axons in the contralateral lateral funiculus of upper cervical segments. These axons were concentrated at the level of the central canal and ventral to it. Craig (1991, 2000) noted that labeled axons appeared to be located in a more ventral position in rostral cervical segments than they were at lower segmental levels. Craig (2000) concluded that axons of lamina I cells are located dorsal to those of lamina V neurons throughout much of the length of the cord but appear to be located within overlapping distributions within C1 and C2.

In a previous study (Zhang et al. 2000), it was found that STT axons appeared to shift into increasingly ventral positions as they ascended through mid- and rostral thoracic segments and into the cervical enlargement. In the present study, the STT axons were located in a distribution within the VLF that does not appear to differ from that in which they were located in the cervical enlargement. Thus, it seems that STT axons do not continue to migrate farther ventrally in segments rostral to the cervical enlargement but continue in a position well ventral to that in which they ascend through thoracic segments.

In several previous studies of the organization of STT axons, it was noted that axons from lumbar and sacral spinal cord segments shift laterally as they ascend the length of the spinal cord. Several authors indicated that lumbosacral STT axons were located on the “extreme periphery” of the cervical spinal cord (Walker 1940; Weaver and Walker 1941). We (Zhang et al. 2000) found that in mid-thoracic segments lumbar STT axons were broadly distributed throughout the medial/lateral center of the lateral funiculus. Within the cervical enlargement, lumbar STT axons were found in a significantly more lateral position. The present findings indicate that within C2, lumbar STT axons are located in a distribution extending from the medial/lateral center of the lateral funiculus to the edge of the cord. Therefore, lumbar STT neurons are located laterally within the VLF of C2, but they are not restricted to a narrow layer on the lateral edge of the cord. The present and our previous findings confirm that lumbar STT axons shift laterally as they ascend the length of the spinal cord, but they do not appear to continue to shift laterally as they ascend through the upper cervical cord.

Apkarian and Hodge (1989) reported that the labeling of SDH neurons following thalamic injections of a retrograde tracer was prevented by lesions of the DLF in mid-thoracic segments and that lesions of the VLF in mid-thoracic cord prevented the labeling of STT neurons in the DDH. These and other findings led to the suggestion that there are two distinct components of the STT: one in the DLF, composed primarily of the axons of marginal zone neurons, and another in the VLF, composed of the axons of neurons in the DDH and ventral horn. This conclusion regarding the organization of STT axons in the mid-thoracic cord was supported by our recent findings (Zhang et al. 2000). The present findings suggest, however, that if the same lesions were made in C2, the results would be very different. Our data indicate that lesions of DLF would...
have little, if any, effect on the retrograde labeling of STT neurons and that lesions of the VLF in C2 would probably prevent the retrograde labeling of STT neurons in both the SDH and DDH.

Over the years, the results of a number of clinically effective, histologically confirmed cordotomies in thoracic segments have been presented. Frequently, the lesions were large and extended well dorsally, often above the level of the denticulate ligament (Foerster and Gagel 1932; Gardner and Cuneo 1945; Kahn and Rand 1952; Nathan and Smith 1979; Sweet 1976; White and Sweet 1969). We found (Zhang et al. 2000) that within mid-thoracic segments, lumbar STT axons are located throughout a similarly wide area of the lateral funiculus. In contrast, in C2, the lesions in many clinically effective cordotomies were relatively small, and they were confined to the VLF (Lahuerta et al. 1994; Moffie 1975; Mullan et al. 1963; Nathan 1994). In response to recent anatomical findings suggesting that SDH axons in monkeys ascend in the DLF, Lahuerta et al. (1994) pointed out that following percutaneous cordotomy in C2 “complete relief of pathological pain was observed in cases where the lesion did not extend to the level of the denticulate ligament.” These authors concluded that, “we do not believe that the DLF generally transmits pain was observed in cases where the lesion did not extend to the level of the denticulate ligament.” These authors concluded that, “we do not believe that the DLF generally transmits impulses responsible for pathological pain sensation.”

The results of the present study indicating that STT fibers have migrated into the VLF before reaching C2 are consistent with these clinical observations.

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