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Histometric study of myelinated fibers in the human trigeminal nerve

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Summary

The trigeminal ganglion, roots and the initial portion of the ophthalmic, maxillary and mandibular nerves were dissected in 3 cadavers, to study the number, area and composition of the fascicles, and the density and diameter spectra of myelinated fibers. The total number of fibers (× 1000) was 26 in the ophthalmic, 50 in the maxillary, and 78 in the mandibular division, 7.7 in the motor root and 170 in the sensory root. In all nerves, the histograms of fiber diameter had a bimodal distribution. Cutaneous and muscle nerve fascicles clearly differed in the fiber density and diameter. The ophthalmic and maxillary nerves (cutaneous) had similar fascicles, and their maximum fiber diameter averaged 14.5 μm. Most fascicles of the mandibular nerve (probably cutaneous fascicles) closely resembled those of the ophthalmic and maxillary nerves, but in some fascicles (probably muscle nerves) the fibers were larger, with a maximum diameter of 19.3 μm. The findings in the three peripheral divisions agree with electrophysiological data about sensory and motor conduction in human trigeminal nerves. The observation that the ophthalmic and maxillary nerves have similar fiber spectra indicates that a special fiber composition does not account for the sparing of the ophthalmic division in trigeminal neuralgia. The absence of very large (A alpha) fibers in the sensory root does not support the view that impulses from muscle spindles are conducted along this root.

Introduction

Although the anatomical and functional organization of the human trigeminal system is of great interest, little quantitative data is available on the composition and fiber spectra of trigeminal nerves. Sensory and motor trigeminal evoked potentials, now being studied in man, are providing new information on trigeminal physiology and the pathophysiology of trigeminal neuralgia. In trigeminal nerves, unlike limb nerves, motor conduction is faster than sensory conduction (Cruccu 1986; Cruccu et al. 1987b). Several authors now accept that in symptomatic, as well as in essential trigeminal neuralgia, the primary lesion also involves the large myelinated afferent fibers, most commonly along their course in the retrogasserian root (Selby 1983; Leandri et al. 1988; Cruccu et al. 1990); the pain, however, usually involves the maxillary and mandibular division, but spares the ophthalmic division. Neurophysiological data obtained in patients treated surgically for the relief of trigeminal neuralgia indicate that the fibers from spindles of masticatory muscles – which are traditionally thought to travel in the trigeminal motor root – pass instead in the sensory root (Ferguson 1978; Ongerboer de Visser 1982, 1983).

We studied myelinated fibers of the trigeminal roots and the three divisions, histometrically, in postmortem specimens. The ophthalmic and maxillary nerve fascicles exhibited a similar fiber composition, unlike that of the muscle nerve fascicles of the mandibular division; a similar difference existed between the sensory and motor root.

Materials and methods

Trigeminal nerves were obtained at autopsy, 24 h after death (as required by Italian law), from 3 subjects (two aged 60 and one 46 years) without neurological diseases. After removal of the brain and dura, the trigeminal roots and ganglion were exposed. The roots were cut approximately 10 mm from the surface of the pons; the ophthalmic, maxillary, and mandibular nerves were cut 5 mm distal to their origin from the ganglion (Fig. 1). Care was taken not to stretch and damage the nerve trunks. The motor and sensory roots and the three peripheral branches were cut

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into separate blocks, under a dissecting microscope. The specimens were fixed overnight by immersion in cold 2.5% phosphate-buffered glutaraldehyde, post-fixed in 4% OsO_4 for 3 h, dehydrated in acetone, and embedded in Spurr. Semi-thin (1 μm) sections were cut with an LKB Ultratome. The sections were stained with basic toluidine blue and examined with a Leitz Orthoplan light microscope. The sections were first inspected at low magnification to count the fascicles and look for possible qualitative differences between fascicles. Counts were made from microphotographs at a magnification of × 1000–1300, taken from the upper right quadrants of all fascicles in the motor root or of 12 fascicles in the other nerves.

Approximately 10% of the fibers showed artifacts, or did not run normal to the plane of section, and were therefore excluded from measurements. By means of a Videoplan 2 Kontron semiautomatic analyzer with a digitizer pen, we calculated the area of the fascicle, the fiber density, and external diameter of the fibers; the minimum and maximum diameter were taken at 99% of fibers.

Results

Low magnification inspection of the fascicles of each nerve showed that the fibers were not arranged in a regular pattern: instead of being grouped according to diameter, fibers of different diameter were intermingled. Table 1 summarizes, for each nerve, the total area, the number of fascicles, the total number of myelinated fibers and the mean fiber density. Table 2 summarizes the data on external fiber diameter: minimum, mean, maximum at 99%, and peaks. There were no noteworthy differences between subjects. The histograms of external diameter were bimodal in all nerves. The ophthalmic and maxillary nerves were composed of homogeneous fascicles: all the fascicles had similar fiber spectra. The fascicles in the ophthalmic nerve were smaller than those in the maxillary nerve. The mean total fascicular area was 2.2 mm^2 for the ophthalmic and 4.2 mm^2 for the maxillary nerve, and the total estimated number of fibers was 25000 and 49000, respectively. The two divisions were, however, similar in all other respects. The data for the ophthalmic and maxillary nerve were respectively: mean number of fascicles 29 and 27, fiber density 11700/mm and 11800/mm, minimum fiber diameter 0.85 μm and 0.9 μm, medium diameter 6.2 μm and 6.7 μm, and maximum diameter 14.8 μm and 14.5 μm.

The mandibular nerve had a mean total area of 8.5 mm. It was far larger than the ophthalmic and maxillary nerves, and contained two kinds of fascicles, which were clearly distinguishable even at low magnification inspection. Most fascicles exhibited features similar to the other two divisions (fiber density 12000/mm, minimum diameter 1.2 μm, medium diameter 6.4 μm, maximum diameter 14.5 μm) and were probably of cutaneous or mucosal origin from the lingual and inferior dental nerves (Fig. 2A). The few remaining fascicles had a lower fiber density (4300/mm) and larger fibers (maximum diameter 19.3 μm) and were probably muscle nerve fascicles for the masticatory muscles (Fig. 2B).

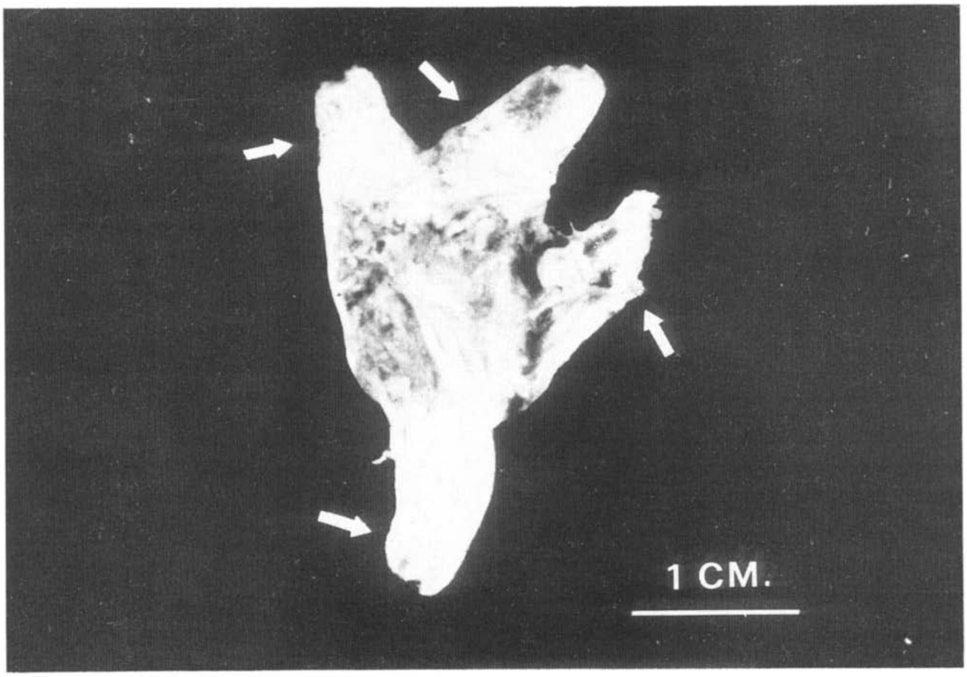

Fig. 1. Trigeminal nerve; the bar indicates the cut section for each division.

TABLE 1

THE TABLE SUMMARIZES, FOR EACH DIVISION, THE TOTAL FASCICULAR AREA, NUMBER OF FASCICLES, FIBER DENSITY, AND ESTIMATED TOTAL NUMBER OF FIBERS.

		Total area (mm^2)	Number of fascicles	Number of fibers	Fiber density (n/mm^2)
Ophthalmic	A	2.5	34	30500	12200
	B	2.0	26	25200	12600
	C	2.1	27	22000	10400
Maxillary	A	4.6	29	52000	11300
	B	4.1	25	47200	12300
	C	4.0	28	50400	11800
Mandibular (total)	A	8.5	35	79500	10800
	B	8.3	15	78200	13000
	C	7.3	15	76450	13000
Sensory fascicles of mandibular n.	A	6.7	33	72300	10800
	B	6.6	13	71024	13000
	C	5.6	12	69300	13000
Motor fascicles of mandibular n.	A	1.8	2	7200	4000
	B	1.7	2	7176	4500
	C	1.7	3	7150	4500
Motor root	A	1.7	4	7650	4500
	B	1.6	4	7840	4900
	C	1.5	4	7500	5000
Sensory root	A	8.5	70	170000	2000

TABLE 2

THE TABLE SUMMARIZES, FOR EACH DIVISION, THE NUMBER OF MEASURED FIBERS AND EXTERNAL FIBER DIAMETERS: MINIMUM, MEAN, MAXIMUM AT 99%, AND PEAKS.

		Number of measured fibers	Diameter minimum (μm)	Diameter medium (μm)	Diameter maximum (μm)	Peaks
Ophthalmic	A	1718	0.8	6.8	15	4.5–12
	B	975	0.9	5.4	14	4.5–10
	C	1474	0.8	6.5	14.5	4.5–9.5
Maxillary	A	1027	1	6.1	13	3.5–9.5
	B	1296	0.9	7.2	15	5.5–9.5
	C	943	0.8	7	16	5.5–10
Mandibular	A	1708	0.8	8.5	18.9	4.5–9
	B	1859	1	7.3	20.3	4–12
	C	1940	1.1	10	18.8	4–13.5
Sensory fascicles of mandibular n.	A	1157	1.17	6.82	15	4.5–10
	B	1414	1.37	5.64	13	3.5–8
	C	1354	1.14	6.88	15	3–9.5
Motor fascicles of mandibular n.	A	200	4.75	12.6	18.8	8.5–14.5
	B	200	3.9	13	20.1	8.5–15
	C	200	4.2	13.1	18.8	8.5–16
Motor root	A	829	2.1	14.6	23	4.5–15.5
	B	853	2.5	14.5	21	4.5–15.5
	C	707	2.9	15	21	8.5–16.5
Sensory root	A	3189	0.3	4.8	11	3–5

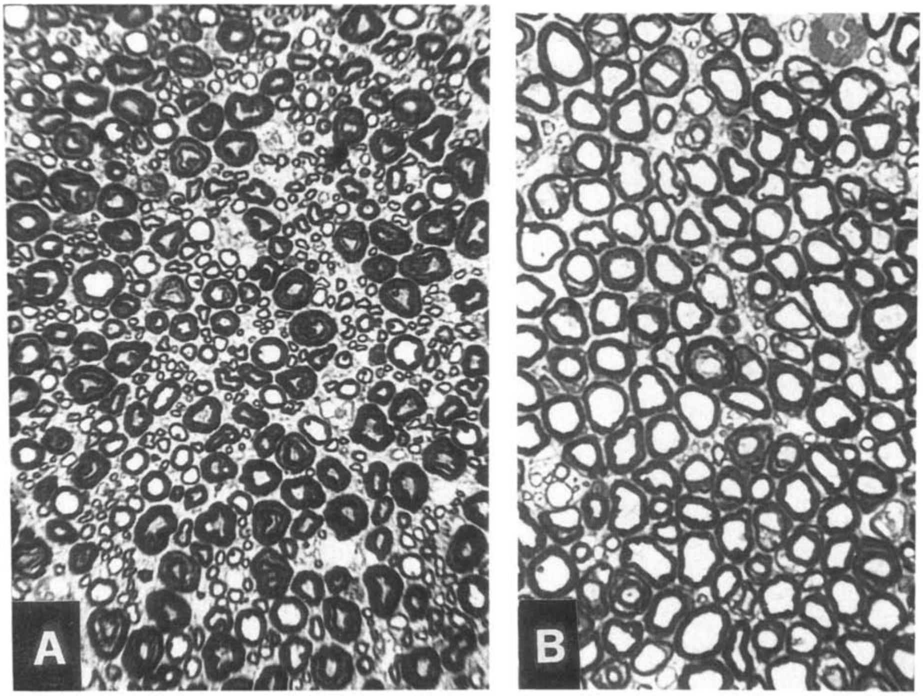

Fig. 2. (A) Detail of a mandibular fascicle probably directed to cutaneous nerves (25 ×). (B) Detail of a mandibular fascicle probably directed to muscle nerves (25 ×).

The motor root in all three subjects was easily identified and processed. It consisted of 4 homogeneous fascicles; the mean total area was 1.6 mm^2, number of fibers 7600, fiber density 4800/mm, minimum diameter 2.5 μm, medium diameter 14.5 μm and maximum diameter 21.6 μm, larger than the diameter measured in the mandibular nerve.

In contrast, because of excessive artifacts in 2 samples we were able to study one sensory root only (subject A in the tables). In this root specimen the total fascicular area was 8.5 mm^2 and the number of fibers was 170000, a value slightly higher than the sum of those calculated in the 3 peripheral divisions (162000). The fibers were smaller in diameter than those observed in the ophthalmic and maxillary division in the same subject: the minimum diameter was 0.3 μm, medium diameter 4.8 μm, and maximum 11 μm (Fig. 3).

Discussion

Despite being a commonly used method (Buchthal and Rosenfalck 1966), histometry has the drawback of possible measurement errors induced by postmortem changes in the nerve axon and its myelin sheath, or by injuries occurring when the nerve is removed from the base of the skull. In our experiments the trigeminal sensory root appeared to be particularly susceptible to damage during removal, possibly because it is provided with very little perifascicular connective tissue. We therefore decided to exclude from the measurement two sensory roots, which displayed excessive artifacts. The remaining specimens contained few damaged fibers. These were easily identified, and excluded from all counts except those of fiber density. Nevertheless, the presence of artifacts should not bias our conclusions. Our aim was not to provide absolute data on fiber diameter for direct comparison with data from other human nerves, but to examine differences in the composition of the trigeminal divisions and roots, in the same individuals, in the same conditions. The few studies on biopsy specimens regard the intra- and extradental nerves only (Johnsen and Johns 1978). A complete histometric study of the trigeminal roots and peripheral divisions in the same human has never been reported, and the one complete animal study (Windle 1926)

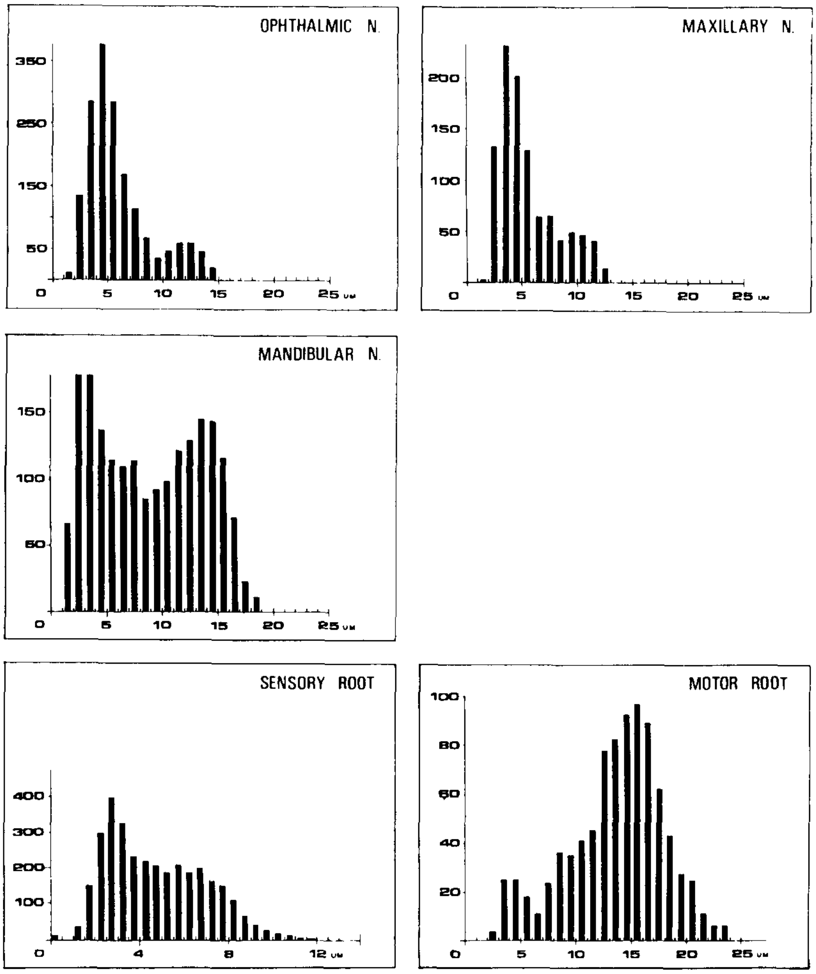

Fig. 3. Histograms of external diameters of myelinated fibers of each division in subject A.

employed paraffin sections, a method no longer in use for nerve morphometry.

The three peripheral divisions

In our samples, the fiber spectra of the ophthalmic and maxillary nerves were almost identical. Both nerves showed a bimodal distribution, with the smaller peak in the range of small myelinated (A delta) fibers and the larger in the range of medium myelinated (A beta) fibers. The fascicles in the ophthalmic and maxillary divisions were homogeneous. We were surprised to find no fascicles with a predominance of small (A delta) fibers as one would expect for the nasociliary nerves innervating the cornea (Lele and Weddell 1959; Rozsda and Beuerman 1979). Our section might have been proximal to the point where the fascicles for the nasociliary nerves separate.

The mandibular division contained two different types of fascicles. One type – similar in all respects to the ophthalmic and the maxillary fascicles – was considered to be of cutaneous or mucosal origin. The second – composed of larger fibers, which reached the range of large myelinated fibers (A alpha) – had a lower fiber density, and was thought to consist of fibers directed to trigeminal muscles.

Histometric studies have been performed on the inferior dental nerve (sensory nerve of the mandibular division) from human cadavers or animals (De Lange et al. 1969; Murphy and Grundy 1969; Rood 1978; Heasman 1984). Rood (1978) found a bimodal distribution, with peaks of 3 μm and 8–9 μm and a maximum diameter of 15 μm. Heasman (1984) also reported a bimodal distribution, with peaks at 3 and 8 μm, values similar to those measured by us in the proximal portion of "cutaneous" fascicles of the mandibular division.

Sensory and motor roots

The only sensory root that we were able to measure consisted of 70 independent, homogeneous fascicles, with a total estimated number of 170000 fibers. The values of diameters were smaller than those found in the cutaneous nerve fascicles of the peripheral divisions. This agrees with Kerr's observation (1967, 1970) that the peripheral process of the ganglionic T-cell is thicker than the proximal process. In no fascicles did we find very large fibers comparable to those of the motor root. Young (1977) studied with electron microscopy the sensory root in one cadaver. The estimated number of myelinated fibers was 62000; even the largest fibers only reach 11 μm in diameter, as in our observations.

In all three subjects the motor root was comprised of low fiber density fascicles. The total number of fibers (7600) was only slightly larger than that in the muscle nerve fascicles of the mandibular divisions. The values of maximum fiber diameter in the motor root were larger than those found in the muscle nerve fascicles of the mandibular division, presumably because of progressive thinning of nerve fibers in their course toward periphery. The lower peak and minimum diameter, larger than that in the cutaneous nerves, were compatible with A gamma efferent fibers.

Using light and electron microscopy Young and Stevens (1979) studied the motor root in 5 cadavers. In their specimens, the estimated number of myelinated fibers varied from about 2000–6500, and the fibers were smaller than they were in our samples: the diameter histogram had a bimodal distribution, with peaks at 2–6 μm and 8–12 μm, and a maximum diameter of 14 μm, although occasional fibers were as large as 16–18 μm in diameter.

Histometric-electrophysiological correlations

In mixed nerves of the limb, sensory conduction velocity is as high as motor velocity. Even in purely cutaneous nerves, such as the sural nerve, the conduction velocity attains 50–62 m/sec (Buchthal et al. 1984; Cruccu et al. 1987b). The conduction velocity of trigeminal nerves is not measured routinely with traditional methods, because the peripheral nerve branches lie for most of their course in the depth of craniofacial structures. The available data have been obtained recently by intracranial stimulation of or recording from the trigeminal roots. Trigeminal sensory nerve conduction velocity has been estimated as 52 m/sec for the ophthalmic and 54 m/sec for the maxillary division, in the portion between the petrous bone and the supraorbital and infraorbital foramina (Cruccu et al. 1987b). Trigeminal motor nerve conduction velocity has been estimated as 55–68 m/sec in the portion between the clivus and the foramen ovale (Cruccu 1986). The difference in conduction velocity between the sensory and motor trigeminal fibers is paralleled by a similar difference in the fiber size. The largest diameters in our specimens were 14–15 μm in the sensory, and 18–19 μm in the motor fascicles.

Considerations on the pathophysiology of trigeminal neuralgia

The most commonly reported causes of "symptomatic" trigeminal neuralgia are vascular anomalies in the posterior fossa and benign tumours of the cerebello-pontine angle (both impinging on the trigeminal sensory root; see Selby (1984) for a review). On the basis of neurophysiological findings, some authors believe that in both "symptomatic" and 'idiopathic" trigeminal neuralgia, a chronic compression produces a demyelinating process in the large myelinated (A beta) afferents, along their course in the root, with possible ephaptic transmission to small diameter nociceptive afferents (not examined in the present paper) or with reorganization of wide dynamic range neurons of the spinal trigeminal nucleus (Burchiel 1980; Calvin et al. 1982; Leandri et al. 1988; Cruccu et al. 1990; Fromm et al. 1984).

Pain in the ophthalmic territory is unusual in "idiopathic" trigeminal neuralgia (Selby 1984). A possible explanation could be that the ophthalmic division exhibits an unusual fiber composition. Yet we found no noteworthy difference between the myelinated fiber spectra of the ophthalmic, maxillary, and mandibular "cutaneous" nerve fascicles. Either the primary site of lesion in idiopathic trigeminal neuralgia is more peripheral, or the ophthalmic division is spared because of its position in the root. The somatotopic organization is probably maintained in spite of prominent anastomosis, and the ophthalmic fascicles remain in dorsomedial position from ganglion to pons. The dorsomedial side of the root might be protected from direct contact with vascular anomalies or other sources of compression.

Finally, in our three specimens, perifascicular connective tissue was very scarce in the sensory roots. By making the nerve fibers of the sensory root more susceptible to damage by compression or stretching, this lack of protection could be important in the pathogenesis of trigeminal neuralgia. Spinal roots are also poor in connective tissue (Thomas and Olsson 1984), but we are not aware of a comparative study of spinal and trigeminal roots in man.

The route of afferent fibers from spindles

In lower mammals, the Ia afferents from muscle spindles of jaw-closing muscles run in the mandibular nerve, continue in the motor root, and enter the pons; the cell bodies are not in the ganglion but in the mesencephalic nucleus (Darian-Smith 1970). A similar pathway has been traditionally accepted for humans (McIntyre and Robinson 1959). Ferguson (1978) and Ongerboer de Visser (1982), however, have found the jaw jerk to be absent in patients submitted to surgical lesions to the sensory root for the relief of trigeminal neuralgia. On this basis, they have suggested that in man the afferents from spindles run in the sensory root and not in the motor root (Ongerboer de Visser 1983).

Histometric data do not support this view. Although Young (1979) and Young and Stevens (1979) could not compare the two roots in the same cadaver, they found that the largest fibers in the sensory root were decidedly smaller than those in the motor root. The sensory root in our samples had a maximum diameter of 11 μm, compared with 23 μm in the motor root and 19 μm in the motor fascicles of the mandibular nerve, in the same cadaver (Table 2, subject A). Sensory roots therefore, appear not to contain the very large A alpha fibers. Given the large number of fibers in the sensory root, we might have missed the few Ia afferents from spindles, only, however, if they had been scattered amongst in different fascicles. This is most unlikely.

The loss of the jaw-jerk after surgery aimed at the sensory root might be due to an insufficiently selective lesion, which also produced unwanted damage to motor root fibers. The very large afferents from spindles are highly susceptible to compression, and damage even to a few fibers is sufficient to abolish the tendon reflex (Cruccu et al. 1987a). Alternatively, spindle afferents may pass to the sensory root through an anastomosis proximal to the point where our sections were cut.

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