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## A dorsolateral spinothalamic pathway in cat

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A spinothalamic tract that courses in the dorsolateral funiculus of the spinal cord and originates almost exclusively from spinal lamina I neurons has been demonstrated in the cat by retrograde transport of horseradish peroxidase. This tract is of special interest because the course of this predominantly lamina I, contralateral projection lies outside the classical course of the spinothalamic tract and because most lamina I cells contributing to the spinothalamic tract have been shown by other investigators to respond exclusively to somatic noxious stimuli. This newly described tract has important implications in the processing of noxious stimuli.

The spinothalamic tract (STT), classically considered to be confined to the ventral quadrant of the spinal cord<sup>17</sup>, conveys nociceptive and other sensory inputs<sup>22</sup> from the periphery to the thalamus. The STT has been described to be made up primarily of axons from cells within contralateral spinal laminae I and IV–VIII<sup>4,23</sup> which cross segmentally in the spinal cord and project predominantly to nucleus submedialis, the centrolateral nucleus, the ventral lateral nucleus and the ventral posterior lateral nucleus of the thalamus<sup>12,13</sup>. In 1937, Kuru inferred from human anatomical studies that lamina I was an important part of the pain–temperature pathway<sup>11</sup>. This has been substantiated by Christensen and Perl who identified lamina I cells in the cat which respond exclusively to noxious stimuli (nociceptive specific cells)<sup>5</sup>. It has been shown in the cat that most STT lamina I cells are nociceptive specific and many bifurcate, terminating in both medial and lateral thalamic nuclei<sup>6</sup>. In fact, cells within lamina I that respond to a broad range of innocuous and noxious stimuli (wide dynamic range cells) generally do not project directly to the thalamus<sup>6</sup>.

Section of the ventrolateral quadrant of the spinal cord has been used since 1911 for the relief of intractable clinical pain<sup>18</sup>. However, the effects of ventrolateral cordotomy are often incomplete or transient, leading one to conclude that either the STT is not dis-

cretely localized, or that alternate pathways for pain transmission exist<sup>3,7,21</sup>. In 1954, Kennard demonstrated that in the cat the dorsolateral spinal pathways are instrumental in the perception of pain since it was only when this area was ablated that behavioural responses to painful stimuli were abolished<sup>9</sup>. Even so, attempts to anatomically demonstrate a feline dorsolateral projection to the thalamus using degeneration techniques have been unsuccessful<sup>2</sup>.

Recent anatomic investigations in this laboratory have shown that cat spinal lamina I cell projections ascend predominantly in the contralateral dorsolateral quadrant of the spinal cord<sup>1</sup>. These experiments showed that lesions of the ventral quadrant of the spinal cord do not block retrograde filling of spinal lamina I cells and dorsolateral quadrant lesions almost totally block transport to lamina I after injection of horseradish peroxidase into the ipsilateral hemicord at levels rostral to the lesion. The present study was designed to investigate whether lamina I cells project to the feline thalamus through the dorsolateral quadrant.

Twelve adult cats were used in these experiments. They were anesthetized with Nembutal (35 mg/kg, i.v.) and operated upon under sterile conditions. Following surgical section of the mid-thoracic ventral quadrant of the spinal cord, a total of 1  $\mu$ l of 2% horseradish peroxidase–wheat germ agglutinin

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(HRP-WGA) was injected stereotactically via a 1- $\mu$ l Hamilton syringe into the thalamus of 7 cats ipsilateral to the lesion. Multiple injections were used to include nucleus submedius, the centrolateral nucleus, the ventral lateral nucleus, and the ventral posterior lateral nucleus<sup>8</sup>. Similar injections were made in 5 control cats without prior ventral quadrant lesion. Following a 3–5-day survival period, the animals were perfused with a 1% paraformaldehyde, 1.25% glutaraldehyde solution and alternate, transverse sections (80  $\mu$ m) of spinal cord from the lumbar (L5-S1) and cervical (C6-T1) enlargements were reacted with tetramethyl benzidine (TMB) as described by Mesulam<sup>15</sup>. Consecutive horizontal (coronal) sections cut from the lumbar enlargements of some control animals were similarly processed. Transverse sections of the thalamus were reacted with TMB and the injection sites were determined. The extent of the ventral quadrant lesions was determined histologically. HRP-labeled cells in the lumbar and cervical enlargements were identified and mapped using light- and dark-field microscopy. HRP-labeled fibers were counted and mapped within a 1-mm band across each of the horizontal serial sections in order to determine the funicular courses of axons transporting HRP.

These experiments resulted in two main findings: (1) retrogradely transported HRP from the thalamus fills contralateral lumbar spinal lamina I cells despite ablation of the classical STT via a thoracic ventral quadrant lesion; and (2) horizontal sections of the lumbar enlargements demonstrate a definite group of labeled fibers in the dorsolateral quadrant contralateral to HRP-labeled lamina I cells.

Thalamic injections included nucleus submedius and the centrolateral, ventral lateral, and ventral posterior lateral nuclei. The rostral extent of the injection occasionally included the caudate nucleus. Extension of HRP from the injection site to the rostral midbrain was either very light or totally absent with no appreciable difference in the distribution of HRP-labeled cells in the spinal cord in either case. Laterally, the injection occasionally included the internal capsule.

In control experiments, labeled cell populations in the lumbar enlargement were found in lamina I, laminae IV–VI, and clustered at the borders of laminae VII, VIII and X (Fig. 1A). A similar distribution of

labeled cells was found in the cervical enlargement (Fig. 1C). The distribution of labeled cells in the cervical enlargement was not affected by lesions in the thoracic cord. The total percentage of laminae IV and V cells in the lumbar enlargement was higher than previously reported in several of our experiments. In these cases the overall cell distribution was similar to that of the monkey<sup>23</sup>. In control animals with 5-day survival times, the number of labeled lamina I cells per section in the lumbar enlargement approximated that of the cervical enlargement.

In animals with thoracic ventral quadrant lesions, heavily labeled lamina I cells represent nearly all of the labeled neurons in the lumbar enlargement contralateral to the thalamic injection site (Fig. 1B and E). In some animals labeled lamina I cells were clustered in groups of 3–6 just medial to the dorsal root entry zone with other lamina I cells interspersed rostrocaudally between the clusters (Fig. 2A and B). Lamina I cells comprised 61–100% of the contralaterally labeled populations in the lumbar spinal cord of lesioned animals, but only 16–26% in controls. The absolute number of labeled lamina I cells per section is not appreciably altered by the presence of a ventral quadrant lesion (Fig. 1). In two of the lesioned animals with 5-day survival times, the number of labeled lamina I cells per section in the lumbar enlargement approached that of those in the cervical enlargement (Fig. 1B and C). The other contralaterally labeled cells were concentrated in laminae IV–VI and at the interface of laminae VII, VIII and X. Lesser numbers of ipsilateral labeled cells were found in the same areas. Five to 10% of labeled lamina I cells were found ipsilaterally in control and lesioned animals.

The portion of intact dorsolateral quadrant varied from lesion to lesion. Those lesions which resulted in ablation of the ventral aspect of the dorsolateral quadrant were associated with higher percentages of lamina I cells in the total labeled population.

Examination of all horizontal sections at the level of the lumbar enlargement under dark-field microscopy revealed a large number of gossamer HRP-filled fibers in the dorsolateral and ventrolateral white matter ipsilateral to the injection site and contralateral to labeled cell bodies (Fig. 2C). There was one labeled fiber in the dorsal columns and there were four labeled fibers in the dorsolateral white

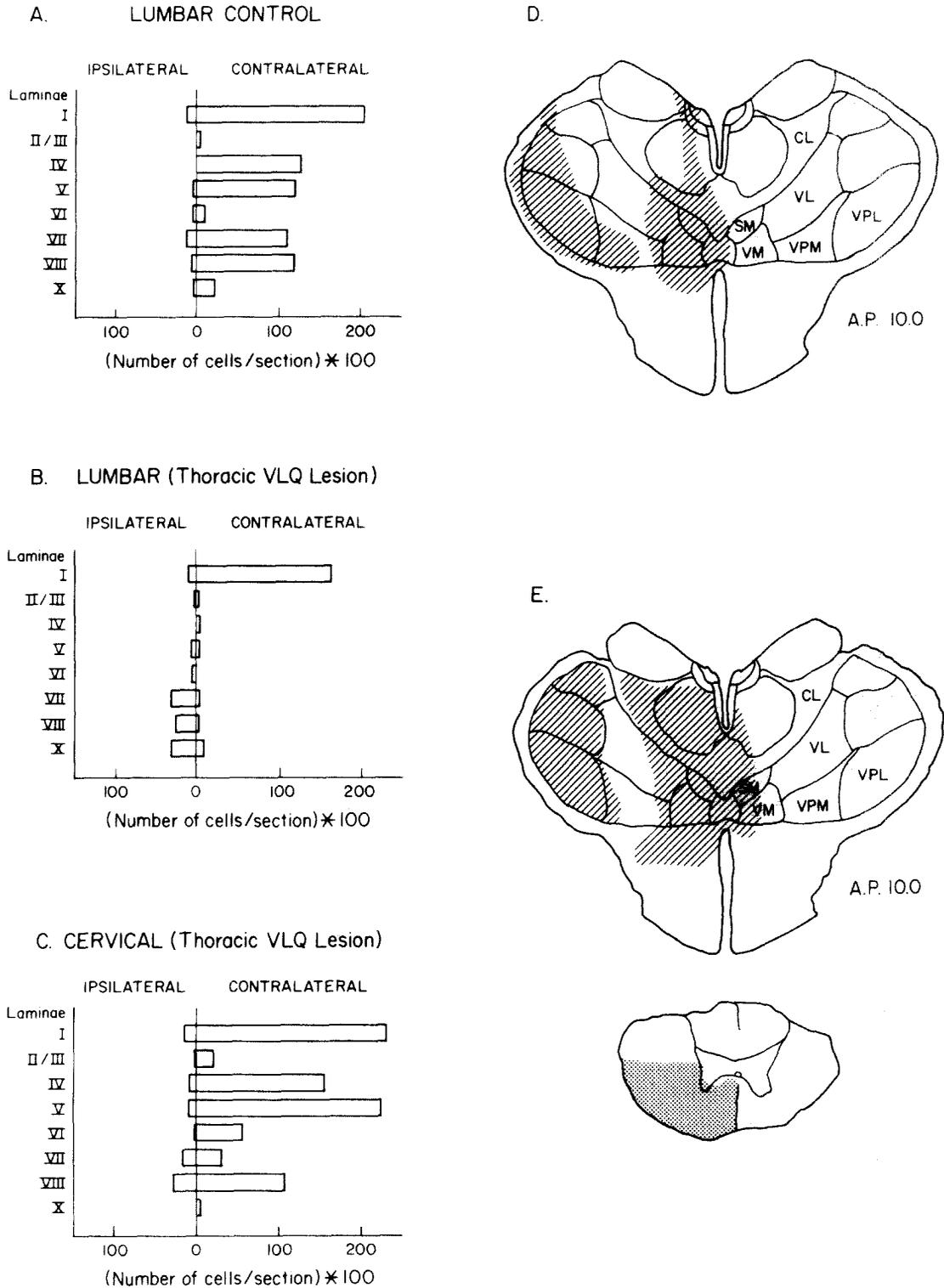


Fig. 1. A: the distribution of HRP-labeled cells within different laminae of the lumbar enlargement from 119 transverse sections, ipsilateral and contralateral to a thalamic injection in a non-lesioned animal. B and C: the distribution of HRP-labeled cells in the lumbar (115 sections) and cervical enlargements (40 sections), respectively, of an animal with a mid-thoracic ventral quadrant lesion. D: injection sites for A (indicated by shaded area) at stereotaxic coordinates AP 10.0 (according to Jasper<sup>8</sup>). E: thalamic injection sites (indicated by shaded area) at AP 10.0, and thoracic lesion of the ipsilateral ventral quadrant (indicated by dotted area) for data presented in B and C. CL, nucleus centralis lateralis; SM, nucleus submedius; VL, nucleus ventralis lateralis; VM, nucleus ventralis medius; VPL, nucleus ventralis postero-lateralis; VPM, nucleus ventralis postero-medialis.

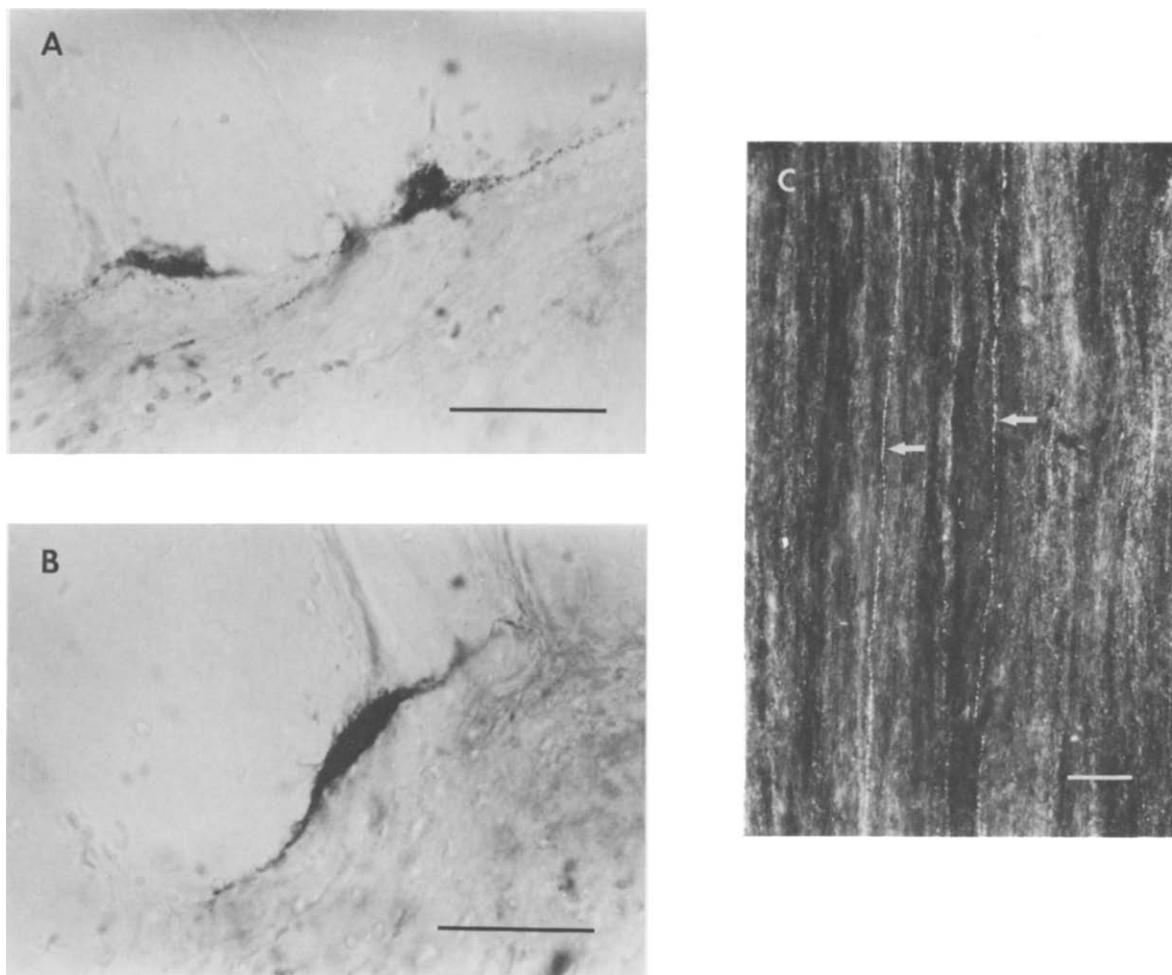


Fig. 2. A and B: HRP-labeled lamina I cells in the lumbar enlargement contralateral to a thalamic injection and a mid-thoracic ventral quadrant lesion. Waldeyer, fusiform and pyramidal cells were seen. Long diameters ranged from 12 to 45  $\mu\text{m}$  with a mode of 24  $\mu\text{m}$ . C: a horizontal section showing HRP-labeled fibers within the lumbar dorsolateral white matter ipsilateral to a thalamic injection. Arrows indicate labeled fibers. Bar equals 50  $\mu\text{m}$ .

matter contralateral to the injection site. This implies that most of these fibers cross segmentally within the spinal cord. Fibers ipsilateral to the injection site were distributed into two groups. One group was located dorsal and the other ventral to the posterior commissure of the spinal cord (Fig. 3). These fibers are not manifestations of anterograde filling of corticospinal axons as there was minimal encroachment of HRP upon the internal capsule and even with such encroachment labeled fibers would be present contralateral to the injection site.

Recent experiments have shown that the majority of ascending lamina I neurons project through the dorsolateral quadrant of the spinal cord<sup>1</sup>. The pres-

ence of approximately equal numbers of labeled lamina I cells per section in the lumbar enlargement of control animals and in the cervical and lumbar enlargements of animals with thoracic ventral quadrant lesions suggests that a majority of lamina I cells projecting to the thalamus travel through the dorsolateral quadrant. The bimodal distribution of labeled fibers, along with the histology of the lesion sites, serves to demonstrate that this tract is not a dorsal extension of the ventrolateral STT.

These experiments demonstrate a previously undescribed spinothalamic pathway composed primarily of lamina I neurons which cross segmentally and project in the dorsolateral quadrant of the spinal

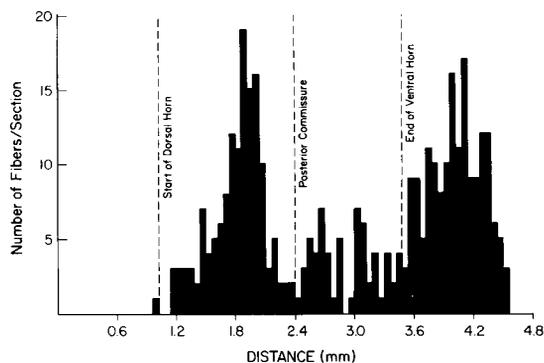


Fig. 3. Distribution of HRP-labeled fibers within the lumbar white matter ipsilateral to a thalamic injection in a single control animal. One labeled fiber was present within the dorsal column (distance, 0.0–1.0 mm from dorsal surface). Concentrations of labeled fibers were located within the DLF (1.0–2.4 mm from dorsal surface) and within the ventral white matter (2.4 mm to ventral surface).

cord. Considering recent work demonstrating the nociceptive specificity of most lamina I cells projecting to the thalamus, this contralateral ascending pathway is likely involved in the transmission of nociceptive information<sup>6</sup>.

The presence of a dorsolateral STT in the cat provides an anatomic basis for the behavioral findings of Kennard<sup>9</sup>. Physiologic investigation of the rat has shown a contralateral lamina I projection from the lumbar to the cervical spinal cord through the dorsolateral quadrant<sup>14</sup>. Some of these lamina I cells<sup>14</sup>

were nociceptive specific and could represent a projection to the thalamus<sup>6</sup>. In a primate study to determine spinal pathways critical for the return of pain sensation after ventral cordotomy, Vierck found that lesions of the dorsolateral quadrant, after the initial analgesic effects of ventrolateral cordotomy had subsided, resulted in transient analgesia for up to a month, but concluded that dorsal spinal pathways are ultimately not critical for the long-term recovery of pain sensitivity<sup>20</sup>. Post-mortem correlation of clinical findings with neuropathologic lesions in 24 humans after percutaneous cordotomy revealed that 3 of 5 lesions localized to the dorsolateral quadrant resulted in contralateral analgesia and pain relief with no ipsilateral weakness<sup>10,16,19</sup>. In view of our findings, this could be interpreted as evidence for the presence of a dorsolateral STT in man. Investigations are currently underway to further elucidate this pathway in the cat and monkey.

This separate dorsolateral spinothalamic projection provides a means to independently investigate the input of lamina I to the thalamus. It is also a potential model for a nociceptive specific ascending system. The existence of this pathway has obvious implications in the treatment of clinical pain.

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