

Changes in the effects of stimulation of locus coeruleus and nucleus raphe magnus following dorsal rhizotomy

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The effects of stimulating locus coeruleus (LC) and nucleus raphe magnus (NRM) on lumbar dorsal horn cells that had been denervated by dorsal rhizotomy were studied. Both LC and NRM stimulation inhibited the responses of dorsal horn cells from the side of the cord with intact dorsal roots. However, when cells from the side of the spinal cord that had had prior rhizotomies were studied, half of the units were shown to be activated by either LC or NRM stimulation.

Spinal deafferentation causes dorsal horn cell hyperactivity in both humans¹⁴ and other species^{15,16}. Deafferentation leads to clinical pain syndromes at times^{14,19,20,25}, and has been used to create experimental pain models^{1,4,17}. Deafferentation pain is poorly responsive to opiates¹⁸ and at times is made worse by opiate injections. Stimulation of brain sites, such as the periventricular grey, associated with opiate analgesia likewise is ineffective in controlling deafferentation pain (personal communications, Richardson, D., 1983). Stimulation of either locus coeruleus (LC) or nucleus raphe magnus (NRM) causes preferential inhibition of dorsal horn cell responses to noxious skin stimulation^{6,7,9,11,12,24}. The study described here was undertaken to determine if LC and NRM modulation of dorsal horn cell activity is altered by spinal deafferentation.

Seven cats underwent unilateral section of lumbar dorsal roots 3–6 under barbiturate anesthesia. Two weeks following rhizotomy the cats were anesthetized with chloralose, paralyzed with gallamine triethiodide, and the lumbar cord was exposed. Blood pressure, end expiratory CO₂, and body temperature were maintained within acceptable limits⁹. Following occipital craniectomy, parylene-coated tungsten stimulating microelectrodes were placed in LC ipsilateral to the rhizotomy and in NRM. Extracellular recordings were made from 110 cells with parylene-coated microelectrodes (2–3 mΩ) from both the intact and deafferented sides of the lumbar spinal cord.

Units from the intact side of the spinal cord were characterized by their responses to peripheral stimulation. Particular attention was paid to those cells on the deafferented side which exhibited periodic high frequency activity. When cells responding to noxious skin stimulation were found, they were activated by either pinch or cutaneous temperature greater than 45 °C. Effects of LC and NRM stimulation on either spontaneous activity, in the cells without receptive fields, or activity elicited by noxious skin stimulation were then determined. A PDP 11/34 computer was used for data collection and analyses as previously described⁷. Brainstem stimulation consisted of 5-s trains of biphasic pulses lasting 200 μs with frequencies of 100 Hz and amplitudes between 100 and 200 μA. Inhibition and facilitation were considered to occur when a clear subjective decrease or increase in the ongoing firing rate of the cell was found and was sustained for the duration of the brainstem stimulation. When inhibition was found, there was usually a very brief period (100–200 ms) of increased activity which preceded the sustained decrease in activity. Locations of stimulating and recording sites were marked by making small electrolytic lesions. At the end of each experiment, the brainstem and spinal cord were fixed in 10% formalin and appropriate 60 μm frozen sections were stained with cresyl violet and the lesion sites determined.

On the control (intact) side of the spinal cord, the effect of LC stimulation upon responses of dorsal

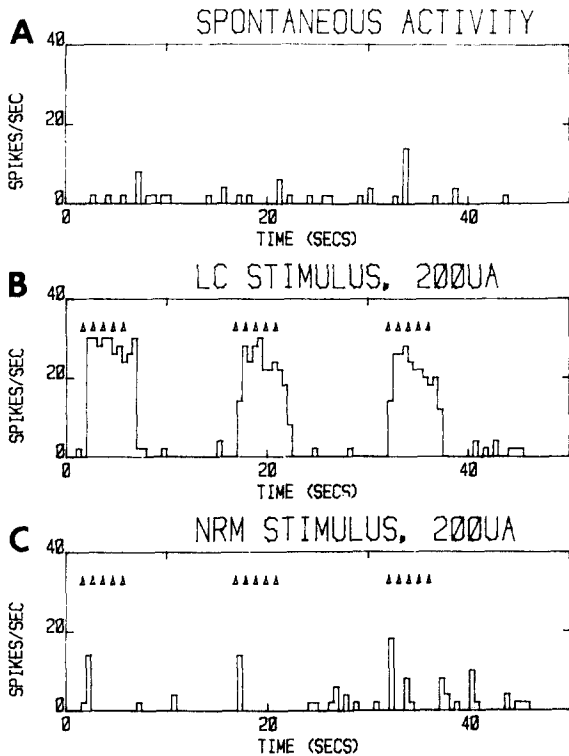


Fig. 1. A: time histogram of the ongoing spontaneous activity of a lamina 4 cell on the deafferented side of the spinal cord. The cell is not responsive to cutaneous stimulation. Note the unit fires with a periodic high frequency pattern. B: stimulation in LC causes a dramatic sustained increase of the ongoing activity of the unit. C: stimulation in NRM inhibits the ongoing activity of the unit. Note the initial phasic excitation of the unit at the start of the NRM stimulation. Triangles show the duration of the brainstem stimulation times.

horn cells to noxious cutaneous stimulation was determined in 11 cells. LC stimulation inhibited the responses of 10 of these cells to noxious skin stimulation and had no effect on one of the cells. The effect of NRM stimulation was determined on the same 11 cells, and caused inhibition of the responses of 8 of these and had no effect on 3 of the cells. There was no sustained facilitatory effect on the spontaneous activity of any of these cells, all of which were located in lamina 4 or 5 (Fig. 3). This data, similar to previous studies^{7,8}, indicates that the primary effect of LC or NRM stimulation on intact dorsal horn cell responses to noxious input is inhibitory.

Ninety cells were recorded from the deafferented side. Only the 38 cells, located in lamina 4–5 of the denervated side of the cord, were used for data analysis. Cells located deeper than lamina 5 were excluded since the effect of LC and NRM stimulation

on deeper cells is frequently facilitatory (6–8,22). Nineteen of these cells showed sustained increased activity consequent to either LC or NRM stimulation (Figs. 1 and 2). The effects of NRM and LC stimulation on these cells were always opposite such that if the unit under study was activated by LC stimulation, it was either inhibited or unaffected by NRM stimulation and if activated by NRM stimulation, it was either inhibited or unaffected by LC stimulation. The remaining 19 cells were either inhibited or unaffected by NRM or LC stimulation. These results are tabulated in Table I. Fig. 3 shows the recording and stimulation sites. Despite rhizotomy, 11 of these dorsal horn cells still had receptive fields. The presence or absence of receptive fields was unrelated to the effect of brainstem stimulation on the cells of the deafferented spinal cord.

The cells that were included in this study on the side of the rhizotomy were assumed to correspond to

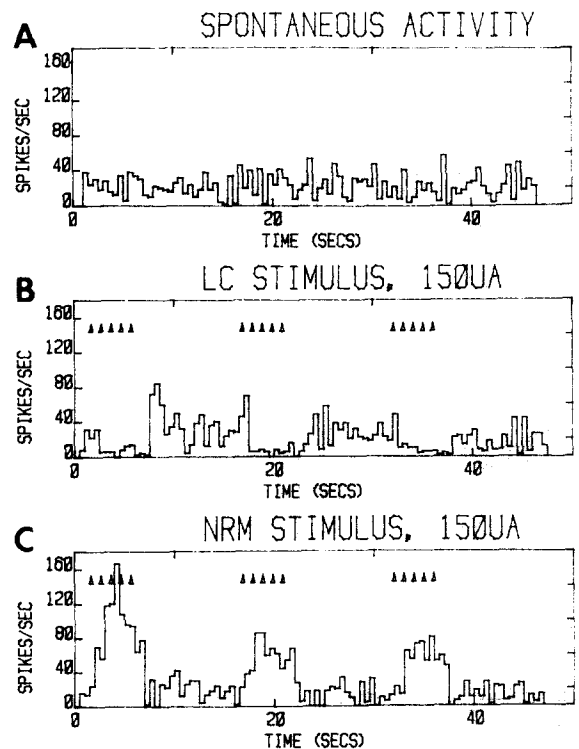


Fig. 2. A: time histogram of the ongoing spontaneous activity of a lamina 5 cell on the deafferented side of the spinal cord. The cell is not responsive to cutaneous stimulation. B: stimulation in the LC region inhibits the ongoing activity of the unit. C: stimulation in the NRM region facilitates the ongoing activity of the unit. Triangles show the duration of the brainstem stimulation times.

TABLE I

	<i>LC</i>			<i>NRM</i>		
	<i>Facil.</i>	<i>Inhib.</i>	<i>No eff.</i>	<i>Facil.</i>	<i>Inhib.</i>	<i>No. eff.</i>
Intact	0	10	1	0	8	3
Rhiz	11	19	8	8	18	12

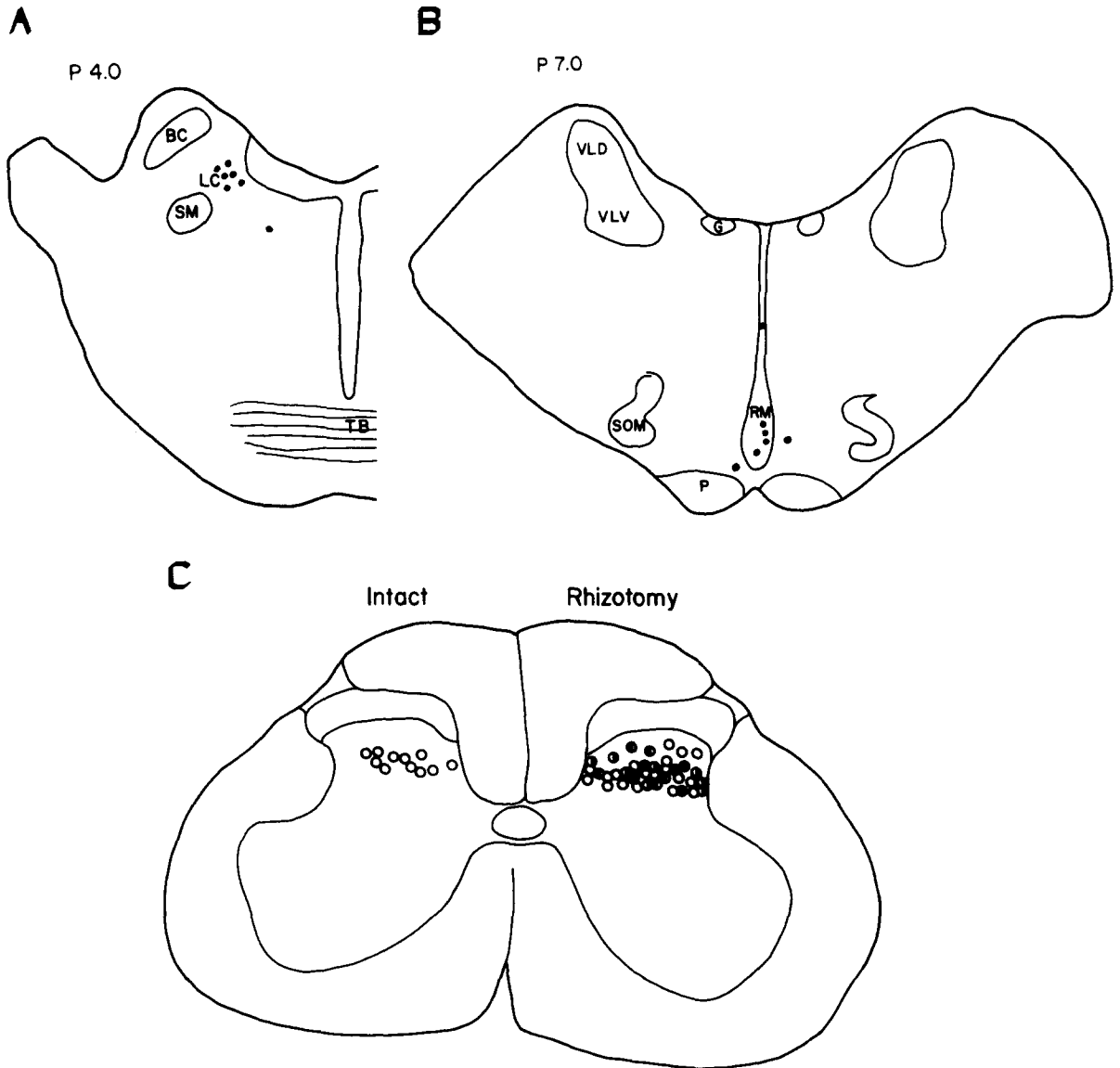


Fig. 3. Stimulation and recording sites in the brainstem and spinal cord. A: position of the stimulating electrode in the area of LC compiled from 7 cats. B: position of the stimulating electrode in the area of NRM compiled from 7 cats. C: locations of the recording electrode in the lumbar dorsal horn from both the intact and rhizotomized sides of the spinal cord. Cells that were facilitated by NRM and inhibited or unaffected by LC stimulation — ●. Cells that were facilitated by LC and inhibited or unaffected by NRM stimulation — ○. Cells that were inhibited or unaffected by both LC and NRM stimulation — ○.

those cells reported previously⁶⁻⁸ from intact animals and to those cells reported here from the control side of the cord. There is no way, however, to be certain that the cells seen in the cord subjected to deafferentation are not from an unique population that is only unmasked following partial denervation. This seems unlikely though in view of the fact that some of these cells had receptive fields and response characteristics to cutaneous stimulation that were indistinguishable from those of cells in intact dorsal horn.

The results of these experiments indicated that the effects of descending bulbospinal pathways on the activity of neurons in partially denervated cat spinal cord are different than those seen in animals with intact spinal cord. The presence of increased activity following either LC or NRM stimulation seen in the cells from the denervated spinal cord was unrelated to the laminar position of the cells in the dorsal horn. Within the denervated portion of the cord, rostrocaudal location of the units studied in relation to the nearest intact nerve root had no predictive value in determining whether or not a cell would respond to brainstem stimulation with increased activity, suggesting that the loss of afferent input consequent to rhizotomy had a non-specific effect on dorsal horn cells. This is substantiated by the fact that neither the presence nor the absence of a response to cutaneous stimulation could be correlated with the occurrence of increased activity following stimulation of LC or NRM. The opposing effects of LC and NRM stimulation suggest differing functional pathways from these two areas to the denervated spinal cord. Whether the two populations of cells, one facilitated by LC stimu-

lation and the second by NRM stimulation, are related to specific functional groups of dorsal horn cells is impossible to determine because of the denervation.

Descending inhibitory effects of both LC and NRM stimulation are mediated, in part at least, by presynaptic mechanisms^{2,11,12,21}. Brief phasic increases in lamina 4 and 5 cell activity are commonly seen after NRM or LC stimulation^{2,7,11,12} preceding the period of inhibition. Further, cells located deeper than lamina 5 can be tonically facilitated following stimulation of these brainstem sites⁶⁻⁸. Therefore, it is clear that both LC and NRM cause a combination of inhibition and facilitation in the normal dorsal horn. It seems a reasonable hypothesis, then, that rhizotomy removes a generalized inhibitory bias on the lamina 4 and 5 cells by interrupting the presynaptic pathways through which LC and NRM exert their influences. Whether the partial loss of the normally potent inhibition of lamina 4 and 5 cells by NRM and LC stimulation is related to the reported loss of opiate receptors³ and substance P^{10,13,23} in the dorsal horn following rhizotomy is uncertain.

Since descending pathways from both LC and NRM have been implicated in endogenous pain control systems⁵, the findings described here might be the physiologic correlate of the difficulty in treating the patient with pain caused by denervation.

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