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Locus coeruleus modulation of dorsal horn unit responses to cutaneous stimulation

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Neurons of the locus coeruleus (LC) and subcoeruleus area have axons which terminate in the spinal cord[10,12,15,20,26]. Terminals of at least some of these neurons contain noradrenaline[1,11,18]. The presence of dense CA terminal concentrations in the apex of the dorsal horn[12,19], alterations in dorsal horn interneuron responses to cutaneous stimulation following intravenous L-DOPA injection[4,16] or iontophoretic application of noradrenaline (NA)[13,25], changes in pain response thresholds after destructive lesions of LC[7], and the apparent interaction of stimulation-produced and narcotic analgesic activity with functioning catecholaminergic systems[2,30] all suggest that noradrenergic brain stem nuclei are able to alter sensory transmission at the dorsal horn level.

In the experiments briefly described here, the functional effects of the LC projection to the lumbar spinal dorsal horn were directly evaluated by determining the changes in dorsal horn cell responses, to noxious and innocuous cutaneous stimulation, caused by electrical stimulation in the region of LC. Eleven cats anesthetized with alpha-chloralose (75 mg/kg) and paralyzed with gallamine triethiodide were used. Blood pressure, end-expiratory CO_2 and core temperature were continuously monitored and maintained within accepted limits[16]. The lumbar enlargement of the spinal cord was surgically exposed and covered with warm saline. A suboccipital craniectomy was done and bipolar stimulation electrodes were placed in the area of caudal LC bilaterally. Target point coordinates used were: posterior 4.0, lateral 2.8, depth –2.8[6,22]. Extracellular recordings from 70 dorsal horn units were done with parylene-coated microelectrodes. Once isolated, the units' receptive fields and adequate stimuli were determined. Unit responses either to innocuous hair or skin displacement with a mechanical stimulator or to heating the skin to noxious temperature levels[8] with a Peltier contact thermode were collected. A PDP-11/34 computer was used for data collection and analysis. The effect of stimulating the ipsilateral or contralateral LC was then determined. Stimulus trains were 250 msec to 10 sec in length. The stimuli were biphasic pulses lasting 200 μsec with a frequency of 100–200 Hz and amplitude varying from 20 to 400 μA. The locations of 20 of the dorsal horn recording sites were marked with

small electrolytic lesions. Lesions were made at all brain stem stimulation sites. At the end of each experiment the animal was perfused with saline and 10% buffered formalin. Appropriate 40 μm frozen sections stained with cresyl violet were examined microscopically to determine the lesion sites.

The predominant effect of LC stimulation was to depress the responses of dorsal horn units located in lamina 4 or 5 to cutaneous stimuli. Sixteen cells which responded only to pinch and noxious thermal skin stimulation were evaluated. For 13 of these 16 cells the effects of LC stimulation were inhibitory. The electrical threshold for these inhibitory effects was usually between 50 and 100 μA. In all animals where the brain stem electrodes were placed satisfactorily in LC, inhibition of the responses to noxious thermal stimulation could be elicited by both ipsilateral and contralateral LC stimulation (Fig. 1). Thirty-two cells that responded to only innocuous stimuli, such as hair movement, were studied. LC stimulation depressed the responses of twenty-four of these cells to innocuous stimulation, increased the responses of three of the cells, and had no effect on five of the cells. Similar effects were elicited by both ipsilateral and contralateral stimulation (Fig. 2). Thirteen cells with graded responses to innocuous and noxious stimuli were studied. LC stimulation depressed the responses to noxious

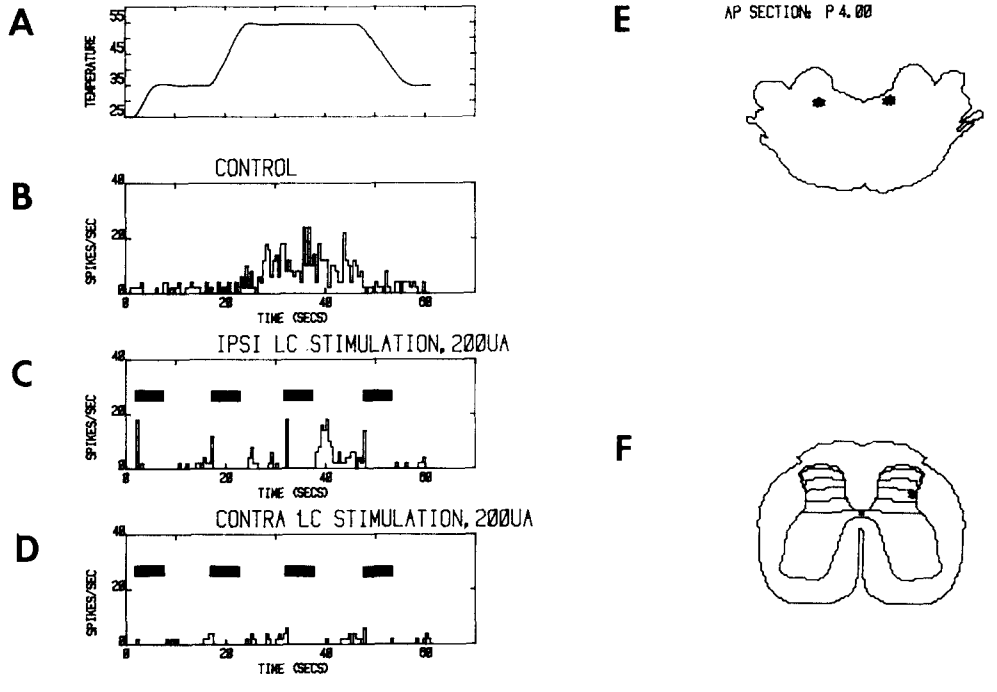

Fig. 1. The effects of locus coeruleus stimulation on responses of a lamina 5 neuron to a cutaneous temperature stimulus. A: the time course and magnitude of the depilated skin temperature change. B: the unit response to the stimulus. Each bin is 0.5 sec wide. C and D: the effects of ipsilateral and contralateral LC stimulation on the response of the unit to the same cutaneous temperature stimulus. The black bars in C and D indicate the time when the brain stem stimulus was being applied. E: the locations of the brain stem electrodes. F: the location of the recording site. The time abscissa in A is the same as in B, C and D.

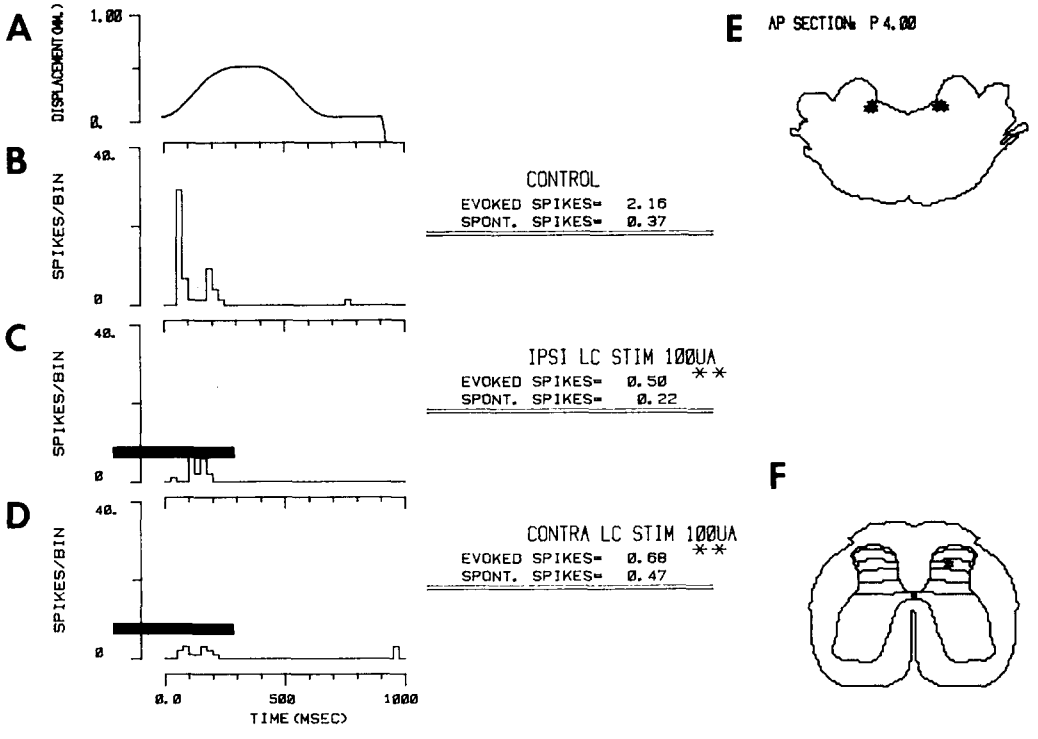

Fig. 2. The effects of locus coeruleus stimulation on the responses of a lamina 4 unit to an innocuous hair movement stimulus. A: the time course and magnitude of the stimulator probe displacement. B, C and D: peristimulus time histograms, each the sum of 20 consecutive trials, showing the average responses of this unit to the cutaneous stimulus. Trials were separated by 5 sec. The average evoked spikes were counted from time 0 to 750 msec after the displacement stimulus onset. C and D: the effects of ipsilateral and contralateral LC stimulation, respectively, the time of which is indicated by the black bars. The double asterisks indicate a significant difference ($P < 0.01$) between the control and test paradigms using the two-tailed t-test. E: the locations of the brain stem stimulating electrodes. F: the location of the recording site in lamina 4. The time abscissae in A, B and C correspond to that of D.

thermal stimulation in 9 of 11 of these cells tested, had no effect on 2 cells, inhibited the responses of 2 cells to innocuous cutaneous stimulation, and increased the response of 2 cells to innocuous cutaneous stimulation. The effects of stimulating ipsilateral and contralateral LC were always similar. Seven cells were found that demonstrated striking increases in activity during either ipsilateral or contralateral LC stimulation (Fig. 3). One of these spontaneously active cells was inhibited by noxious cutaneous stimulation, one was activated by noxious cutaneous heat, and 5 responded only to brisk tap of the hindlimb (Fig. 3). These cells were all located in dorsal horn lamina 6.

These results indicate that the primary effect of the coeruleospinal pathway is inhibitory on responses of lamina 4 and 5 cells, and that deeper lamina 6 cells can be activated by LC stimulation. Studies using retrograde transport of horseradish peroxidase from the cord to LC have shown, but have not emphasized, bilateral[15,28] coeruleospinal projections; our data suggest the existence of functionally similar projections to the lumbar dorsal horn from both loci coerulei. Though LC stimulation presumably

releases noradrenaline (NA)[1] from coeruleospinal terminals, iontophoresis of NA in the dorsal horn causes selective inhibition of interneuron responses to noxious stimuli and has little effect on the responses of dorsal horn cells to innocuous stimuli[5]. Similarly, the effects of intravenous injections of the NA precursor L-DOPA on dorsal horn responses[16] are not mimicked by LC stimulation, even though we have shown in 4 cats pretreated with the amine depletor, reserpine, that LC stimulation is dependent on intact monoamine stores (unpublished observation). Our results are similar to those of Sasa et al.[23,24], who have shown that LC stimulation causes reserpine-sensitive inhibition of the responses of trigeminal interneurons to inferior alveolar nerve stimulation. The profound inhibition described here is consistent with the behavioral analgesia seen when the LC area is stimulated[27], and the apparent partial dependence of narcotic analgesia on functioning catecholaminergic systems[30]. It remains unclear, however, why pain thresholds should increase when LC has been destroyed bilaterally[7], and why stimulation-produced analgesia should be antagonized by increased NA levels in the central nervous system[2]. These conflicts may occur in part because there are other major catecholamine nuclei projecting to the spinal cord[11,18] or because we are looking at indirect effects of NA release, since we are recording primarily from neurons in lamina 4 and 5 and the most prominent dorsal horn concentration of NA is in the apical region[10,12,20]. Furthermore, LC stimulation or pharmacologic alterations

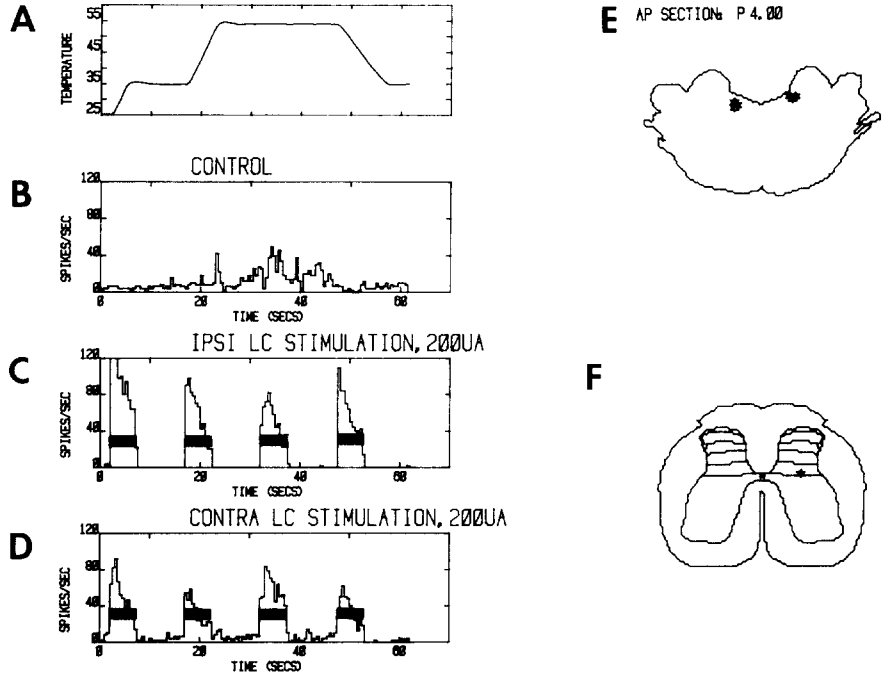

Fig. 3. Activation of a lamina 6 cell by LC stimulation. A: the cutaneous temperature stimulus time course and magnitude. B: the control response to this stimulus. C and D: the effects of ipsilateral and contralateral LC stimulation, the times of which are indicated by the black bars. E: the brain stem stimulation sites. F: the recording site in lamina 6. The time abscissa in A is the same as in B, C and D.

of NA availability may have even more indirect effects because of extensive suprasegmental connections of LC and other catecholaminergic nuclei[21]. There is some suggestion that the function of LC in sensory processing may be confounded by the proximity of the parabrachial nucleus[14]. The role of the LC control of sensory transmission in the functioning animal is uncertain, but is almost certainly more broad than just an analgesic mechanism, since LC receives input from visual, motor, somatosensory, and non-specific brain stem systems[9,17], LC neurons project to spinal cord, cerebellum, hypothalamus, and cerebral cortex[21,29], and NA systems apparently play important roles in such global central nervous system functions as learning, behavior, reaction to stress and sleep[3].

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