Effects of Lateral Reticular Nucleus Lesions on the Exercise Pressor Reflex in Cats

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SUMMARY. Electrical stimulation of ventral roots gives rise to a reflex cardiovascular response similar to that observed during static exercise. Although the afferent limb of the reflex is known to be comprised of small diameter afferent fibers from the contracting muscle, little is known of the central nervous system pathway(s) involved. The lateral reticular nucleus of the brainstem is known to be an important site of integration for numerous types of visceral and somatic afferent information, many of which give rise to cardiovascular responses. However, the linkage between the small diameter muscle afferents responsible for the exercise pressor reflex and the lateral reticular nucleus has not been established. In anesthetized cats (n = 7), stimulation of L7 and S1 ventral roots increased mean arterial pressure (18.6 ± 2.4 mm Hg) and heart rate (7.4 ± 1.7 beats/min). Following bilateral lesions of the lateral reticular nucleus, the increases in mean arterial pressure and in heart rate were essentially abolished (P < 0.005) (mean arterial pressure increased 1.9 ± 0.8 mm Hg and heart rate increased 0.7 ± 0.5 beats/min). Unilateral lateral reticular nucleus lesions and control lesions in pressor sites outside the lateral reticular nucleus (n = 5) did not affect the exercise pressor reflex. The lateral reticular nucleus lesions also produced decreases (P < 0.01) both in resting mean arterial pressure (−27 ± 5.5 mm Hg) and heart rate (−31.0 ± 8 beats/min). These data suggest that the lateral reticular nucleus is important in the central pathway of the exercise pressor reflex and mediates a tonic pressor influence at rest. (Circ Res 51: 400-403, 1982)

IT IS well known that static exercise causes an increase in arterial blood pressure and heart rate. Obviously, while much of the control of these responses is mediated through the central nervous system (CNS), little is known of the precise nature of the neuronal circuitry involved (Shepherd et al., 1981).

Two basic hypotheses exist concerning the pathways responsible for this pressor response, neither of which are mutually exclusive. One hypothesis suggests that "central command" originating in the rostral brain activates the cardiovascular system (Krogh and Lindhard, 1913). The other hypothesis suggests that stimuli originating in the exercising muscles trigger a reflex pressor response (Alam and Smirk, 1937). The latter hypothesis may be conveniently studied in an acute animal preparation in which muscular activity evoked by stimulation of the ventral roots induces an accompanying pressor response. Investigations using this model have indicated that the exercise pressor response is a neurally mediated reflex (Coote et al., 1971; McCloskey and Mitchell, 1972; Mitchell et al., 1977) that is initiated by stimulation of muscle receptors which are supplied by small diameter fibers (McCloskey and Mitchell, 1972). Large diameter muscle afferent fibers apparently play no role in this response (McCloskey et al., 1972).

Since a part of the ongoing research of this laboratory has dealt with the analysis of this experimental model of exercise, it was of interest that Ciriello and Calaresu (1977b) demonstrated that lesions in the lateral reticular nucleus (LRN) abolished pressor responses evoked by stimulation of the central cut end of the sciatic nerve. Recent studies by Kniffki et al. (1981) have shown that, of the higher threshold muscle afferents, only 30% of group IV (unmyelinated) and 40% of group III (fine myelinated) afferents respond to muscle contraction. Hence, stimulation of a mixed nerve such as the sciatic is very nonspecific because all muscle afferents, as well as cutaneous and joint afferents, are activated. Therefore, the present study was undertaken to determine whether lesions of the LRN also abolished the pressor reflex caused by muscle contraction, a stimulus which activates only a selected group of the muscle afferents.

Methods

Adult cats 2.7–3.2 kg were anesthetized with sodium pentobarbital (35 mg/kg). Blood pressure was monitored by a cannula placed in one common carotid artery. Another cannula was placed in an external jugular vein for the infusion of supplemental drugs and fluids.

Using standard laminectomy procedures, we exposed and severed the L7 and S1 ventral roots and set up the peripheral cut end for electrical stimulation on bipolar hook electrodes. The triceps surae muscle was arranged for the monitoring of isometric muscle tension. Following appro-
appropriate craniectomy procedures, a small portion of the caudal cerebellar vermis was removed and stainless steel monopolar semimicroelectrodes (Rhodes SNE-300 tip diameter 0.1 mm) were placed either in the lateral reticular nucleus or other target brain sites using a combination of stereotaxic coordinates (Berman, 1968) and surface landmarks. The lateral reticular nucleus electrode placements were made at the level of the obex. In addition, electrical stimulation (200 μA, 0.5 msec in duration, 50 Hz) of all the target brainstem locations identified them as pressor sites. Control levels of the exercise pressor response were obtained using stimulation of the ventral roots (3X motor threshold, 0.1 msec in duration, 50 Hz). Lesions of the LRN or other pressor sites were made by passing DC current (2.5-5 mA; electrode positive) for 10 seconds. After making the lesions, blood pressure was allowed to stabilize for 30 minutes to 1 hour before the ventral roots were again stimulated using the previous parameters. The effects of those lesions on the exercise pressor response were observed. The lesions were later histologically located after the brainstems were cut in 50-μm sections aided by the use of Prussian blue reagents in fixation procedures. The extent of the lesions was verified by microscopic examination of the sections following Nissl staining with cresyl violet. We have included a histological section in Figure 1 to relate the extent of the electrolytic lesion. Although the currents used may seem high, the damaged areas are actually quite discrete, possibly due to the tip configuration (0.1 mm diameter) of the electrodes.

**Results**

Figure 1 shows a typical result from one animal in which bilateral lesions of the lateral reticular nucleus were made. The muscle contraction caused by ventral

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
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<tbody>
<tr>
<td>Effects of Bilateral Lateral Reticular Nucleus Lesions on the Cardiovascular Responses Evoked by Stimulation of the Ventral Roots</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arterial pressure</th>
<th>Before LRN lesion</th>
<th>After LRN lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>+18.6 mm Hg</td>
<td>+1.9 mm Hg</td>
</tr>
<tr>
<td>se</td>
<td>±2.4</td>
<td>±0.8</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.005*</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart rate</th>
<th>Before LRN lesion</th>
<th>After LRN lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>+7.4 beats/min</td>
<td>+0.7 beats/min</td>
</tr>
<tr>
<td>se</td>
<td>±1.7</td>
<td>±0.5</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.005*</td>
<td></td>
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</tbody>
</table>

* Paired mean difference Student’s t-test (n = 7).
Effects of Bilateral Lateral Reticular Nucleus Lesions on Resting Mean Arterial Pressure and Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>Before LRN lesion</th>
<th>After LRN lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>91.2 mm Hg</td>
<td>73.4 mm Hg</td>
</tr>
<tr>
<td>±s</td>
<td>±8.0</td>
<td>±6.3</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt; 0.01*</td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>133 beats/min</td>
<td>103.3 beats/min</td>
</tr>
<tr>
<td>±s</td>
<td>±8.5</td>
<td>±8.9</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt; 0.01*</td>
<td></td>
</tr>
</tbody>
</table>

*Paired mean difference Student's t-test (n = 7).

The present experiments have demonstrated that the bilateral integrity of the lateral reticular nucleus is important for the expression of the exercise pressor reflex. This result is slightly at variance with that obtained by Ciriello and Calaresu (1977b), since they were able to abolish the pressor response to sciatic nerve stimulation with ipsilateral lesions. The major difference between our study and that of Ciriello and Calaresu appears to be in the method by which peripheral afferent fibers were activated.

The fall in blood pressure and heart rate due to LRN lesions was previously observed in cats by Guertzenstein and Silver (1974). However, a lowered blood pressure has the potential of rendering the animals unable to generate pressor responses. Therefore, in two animals, pressor responses were evoked by stimulation of the brainstem from stimulus sites rostral to the LRN lesions. These responses proved that the condition of the animals had not deteriorated to the point at which a pressor response was impossible due to lowered blood pressure.

The present experiments do not precisely indicate the nature of the LRN's involvement in the exercise pressor response, since lesions do not discriminate between cells and fibers "en passage." Despite this limitation, there is much supporting evidence to suggest LRN's role as a major relay for this response. It is well known that the late component of group III and IV somatosympathetic reflexes relays through the caudal brainstem (Sato and Schmidt, 1973). Furthermore, the projection of the LRN to the cerebellum may also be an important link in this reflex circuitry, since a reduction in pressor responses has been observed in exercising conscious dogs with lesions in the fastigial nucleus (Foreman et al., 1980). The fastigial nucleus has been identified as a pressor site (Miura and Reis, 1969) and LRN has been demonstrated to project both to the fastigial nucleus and to the cerebellar cortex (Matsushita and Ikeda, 1976). The fastigial nucleus, in turn, sends projections to numerous brainstem pressor regions (Moolenaar and Rucker, 1976), including the para-
median nucleus which appears to be the major brainstem relay for the pressor response to fastigial nucleus stimulation (Miura and Reis, 1969). This putative arrangement may be indicative of a type of long loop cerebellar reflex similar to that which Eccles (1967) has envisioned for lower threshold muscle afferents and their interactions in the somatomotor system.

Although we cannot discount the possibility that the effects of LRN lesions may result from simply interrupting fibers passing through the nucleus, a few relationships should be pointed out which indicate that at least some of the related fiber systems having cardiovascular function in the area probably are not involved in producing our observed effects. A descending pressor pathway from the hypothalamus passes around and through (Ciriello and Calaresu, 1977a) and just ventrolateral (Saper et al., 1976) to the LRN. In addition, stimulation of the posteromedial hypothalamic nuclei activates cells in LRN (Ciriello and Calaresu, 1977b). However, interruption of this pathway is not likely to have any effect on the exercise pressor response, since the reflex is obtained (and even enhanced) in a cerebellectomized animal (Coote et al., 1971; McCloskey and Mitchell, 1972). In addition, although there are pressor sites just rostral to the LRN, Dampney and Moon (1980) have suggested, on the basis of their observations in the rabbit, that the efferent projection of these areas does not descend caudalward through the LRN.

Finally, it is important to reemphasize the existence of the descending pressor pathway arising from hypothalamus and passing through the LRN region. This pathway probably indicates that the pressor circuitry utilized during ventral root stimulus-induced exercise is only a part of that which is activated during electrical stimulation of the LRN. An attenuated pressor response may still be obtained to stimulation of LRN in a cerebelllectomized animal as compared to the intact animal (Thomas et al., 1977). This response may be accounted for by activation of the hypothalamic pathway, since it might be activated separately from any of the putative exercise pressor reflex pathways possibly involving the cerebellum.

Thus, the present experiments represent a necessary first step in the elucidation of the central reflex pathway for the exercise pressor response. Further investigations with single cell recordings probably will indicate whether or not the LRN and related nuclear areas respond in a manner appropriate to participate in these responses.

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