Red Nucleus Stimulation Inhibits Within the Inferior Olive

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Horn, K. M., T. M. Hamm, and A. R. Gibson. Red nucleus stimulation inhibits within the inferior olive. J. Neurophysiol. 80: 3127–3136, 1998. In the anesthetized cat, electrical stimulation of the magnocellular red nucleus (RNm) inhibits responses of rostral dorsal accessory olive (rDAO) neurons to cutaneous stimulation. We tested the hypothesis that RNm-mediated inhibition occurs within the inferior olive by using stimulation of the ventral funiculus (VF) of the spinal cord in place of cutaneous stimulation of the hindlimb. Fibers in the VF terminate on hindlimb rDAO neurons, so inhibition of this input would have to occur within the olive. rDAO responses elicited by VF stimulation were inhibited by prior stimulation of the RNm, indicating that inhibition occurs within the olive. In contrast, evoked potentials recorded from the VF or dorsal columns following hindlimb stimulation were not affected by prior stimulation of RNm, indicating that stimulation of the RNm does not inhibit olivary afferents at spinal levels. RNm stimulation that inhibited rDAO responses had little effect on evoked somatosensory responses in thalamus, indicating that inhibition generated by activity in RNm may be specific to rDAO. To test limb specificity of RNm-mediated inhibition, conditioning stimulation was applied to the dorsolateral funiculus at thoracic levels, which selectively activates RNm neurons projecting to the lumbar cord. Stimulation at thoracic levels inhibited evoked responses from hindlimb but not forelimb regions of rDAO, suggesting that inhibitory effects of RNm activity are limb specific. Several studies have reported that olivary neurons have reduced sensitivity to peripheral stimulation during movement; it is likely that RNm-mediated inhibition occurring within the olive contributes to this reduction of sensitivity. Inhibition of rDAO responses by descending motor pathways appears to be a salient feature of olivary function.

INTRODUCTION

Recording from the inferior olive or of complex spikes in cerebellar cortex indicate that neurons within the rostral dorsal accessory olive (rDAO) are very sensitive to somatosensory stimuli such as light touch, hair movement, vibration, and taps (Eccles et al. 1972; Gellman et al. 1983, 1985; Rushmer et al. 1976). Despite their high sensitivity, olivary neurons show little or no increase in discharge during active movement (Armstrong et al. 1982, 1988; Dugas and Smith 1992; Mano 1974; Thach 1968, 1970). Several investigators have hypothesized that olivary neurons are inhibited during periods of movement (Armstrong et al. 1982; Gellman et al. 1985), and subsequent experiments have demonstrated that this is the case (Apps et al. 1990, 1997; Horn et al. 1996a). The reduction of olivary responses during movement might be the result of inhibition of neurons supplying input to the olive, inhibition within the olive, or a combination of both. Because the inferior olive receives dense innervation by GABAergic axon terminals (Nelson et al. 1989), it is likely that at least some of the inhibition occurs within the inferior olive.

Stimulation of the magnocellular red nucleus (RNm) or rubrospinal tract (RST) of the anesthetized cat inhibits responses of rDAO neurons to external stimuli for ~100 ms after the conditioning stimulation (Weiss et al. 1990). Conditioning with short high-frequency pulse trains probably mimics some aspects of neural events that occur in the awake animal during movement, because RNm neurons discharge at high rates during movement, and the discharge occurs in phasic bursts with durations on the order of hundreds of milliseconds (Burton and Onoda 1978; Horn et al. 1992; Padel and Steinberg 1978). rDAO is functionally related to RNm via connections through intermediate cerebellum, and RNm connects the output of intermediate cerebellum to spinal levels (Gibson et al. 1987). It is likely that RNm activity during movement contributes to inhibition of rDAO responses. The primary goal of the present study was to test the hypothesis that RNm stimulation produces inhibition within rDAO.

Regions of rDAO that respond to cutaneous stimulation of the hindlimb receive input via direct and indirect spinal pathways (Berkley and Worden 1978; Boesten and Voogd 1975; Brodal et al. 1950; Ekerot et al. 1979; Molinari 1984). The direct pathway originates from neurons at lumbosacral levels. The axons from these spinal neurons decussate at spinal levels and travel in the ventral funiculus (VF) to terminate in lateral regions of rDAO. Spinal neurons contributing to the major indirect afferent pathway have axons that ascend in the dorsal column and terminate in the gracile nucleus. Axons of the gracile neurons then decussate and terminate in hindlimb regions of rDAO. Figure 1 schematically illustrates the course of both pathways to rDAO.

The VF pathway provides a way to determine whether RNm-mediated inhibition occurs within rDAO, because stimulation of the VF produces monosynaptic activation of rDAO. If conditioning stimulation of the RNm produces inhibition within the rDAO, one would expect responses to VF stimulation to be inhibited. On the other hand, if RNm-mediated inhibition occurs at preolivary sites only, then conditioning stimulation of RNm should have no effect on rDAO responses elicited by VF stimulation.

Our results demonstrate that rDAO responses to VF stimulation are strongly inhibited by conditioning stimulation of the RNm, thereby indicating that inhibition occurs within the rDAO. Additional tests indicate that stimulation of RST fibers terminating at lower spinal levels selectively inhibits rDAO neurons with receptive fields on the hindlimb, and that evoked responses in the ventral basal thalamus are not inhibited by prior stimulation of the RNm. The data suggest that RNm-mediated inhibition is selective for the rDAO and probably serves a function unique to the olivocerebellar system.
with a clamp placed on the dorsal process at T11. The dura was opened for placement of electrodes.

**Recording and stimulation procedures**

Extracellular recordings were made with tungsten electrodes coated with Epoxylute. Recordings were made at an amplifier bandwidth of 300 Hz to 10 kHz. In some cases the low-frequency cutoff was reduced to 100 Hz. Electrodes used for stimulation in the RNm, VF, and dorsolateral funiculus were made from etched 0.5-mm tungsten rods insulated with Epoxylute and had tip exposures of 40–50 μm. A pair of stainless steel wire electrodes bent at right angles for the last 1 mm were used for stimulating the surface of the dorsal columns. Peripheral stimuli were delivered through a pair of 25-gauge hypodermic needles inserted into the skin within the receptive field of the units recorded in the rDAO.

Stimulus pulses were delivered through constant-current stimulus-isolation units. Stimuli delivered to the RNm or RST in the dorsolateral funiculus were delivered in 100-ms trains of 0.1- to 0.2-ms pulses at rates of 100–400 Hz. Current strength was varied in individual experiments to obtain an inhibition of olivary responses to peripheral stimuli and stimuli in the dorsal columns and ventral funiculus; these values are given in RESULTS. Single stimuli were delivered with bipolar electrodes in the dorsal columns, VF, and to peripheral receptive fields. Pulse durations were 0.2–0.5 ms. Current amplitudes varied in individual experiments, as indicated in RESULTS. Stimulus strength was set to elicit an olivary response that was robust but submaximal.

Electrodes were positioned into the RNm and rDAO with the aid of microelectrode recording. RNm neurons were identified by large action potentials and prolonged injury discharge. rDAO neurons were identified by characteristic discharge waveforms, slow irregular spontaneous discharge, and responses to light taps on the limbs (Gellman et al. 1983). After the RNm was identified, the recording electrode was replaced with an array consisting of two to four stimulating electrodes. Slight adjustments were made to the final position to obtain olivary inhibition at the lowest stimulus strengths. In one experiment, recordings were made within the forelimb and hindlimb regions of the thalamic nucleus, ventralis posterior lateralis (VPL). The thalamic recording electrode was positioned to yield maximal multunit responses to peripheral stimulation of the appropriate limb.

The RST was stimulated using a pair of tungsten electrodes inserted into the dorsolateral funiculus at T12. Their position was adjusted to produce the maximum antidromic volley in the RNm. The VF pathway was activated directly via stimulating electrodes placed at T12 ipsilateral to the rDAO. Other modes of rDAO activation included stimulation of the contralateral DC at T12 and cutaneous stimulation of the hindlimb.

**METHODS**

**Surgical preparation**

Experiments were conducted on seven adult cats. A surgical level of anesthesia was induced by intravenous injection of pentobarbital sodium, given to effect (~30–35 mg/kg). A cephalic vein was cannulated for administration of supplemental doses of anesthesia, given as needed (~2 mg·kg⁻¹·h⁻¹). A tracheotomy was performed, and a tracheal cannula was inserted. In some experiments, atropine was injected subcutaneously to reduce airway secretions. Body temperature was monitored and maintained near 37°C. Cats were mounted in a stereotaxic frame, and craniotomies were performed to allow access to the RNm and rDAO. A laminectomy was performed at T12–T13 and the spinal column stabilized.
with a pair of fine forceps. The results of trials following these sections were entirely consistent with those performed before the sections.

At the end of each experiment, recording and stimulation sites were marked with electrolytic lesions (−5 to −10 μA for 5–10 s for recording electrodes; up to +100 μA for 10 s for stimulating electrodes with large tip exposures). The cats were given an overdose of pentobarbital and perfused transcardially with saline, followed by 10% formalin. The brains and sections of spinal cord were frozen, sectioned and stained with neutral red and luxol blue to visualize the tracks and lesions. Figure 2 illustrates marking lesions placed at the recording site in forelimb rDAO (Fig. 2A) and at the caudal RNm stimulating electrode (Fig. 2B) for cat VB-1.

RESULTS

Does RNm-mediated inhibition occur within the rDAO?

INHIBITION OF RESPONSES TO VF STIMULATION. The object of these experiments was to determine whether RNm stimulation inhibits rDAO responses to monosynaptic input via the VF. The hindlimb area of rDAO was identified by recording olivary responses to light cutaneous stimulation of the hindlimb. Once the receptive field of the olivary area was determined, a pair of electrodes was inserted percutaneously into the field. Figure 3A illustrates the evoked response from hindlimb rDAO to stimulation of the foot. The latency of foot shock to rDAO response onset was 19 ms [comparable with the average unit latency of 23 ms for hindlimb rDAO reported by Gellman et al. (1983); midpoint of the rDAO evoked response, which may be closer to an averaged unit response, was 21 ms, Fig. 5C].

Next, a bipolar recording and stimulating electrode was positioned in the ventral funiculus at spinal level T12. Placement of the VF electrode was guided by recording evoked potentials to the cutaneous stimulation site used to elicit the olivary response shown in Fig. 3A. Figure 3B illustrates the

FIG. 2. Confirmation of recording and stimulating sites. A: parasagittal section of the caudal brain stem of cat 7. Electrode tracks can be seen above rDAO. Arrow marks the location of a lesion (−10 μA, 10 s) within the forelimb portion of rDAO. B: parasagittal section illustrating the midbrain contralateral to the inferior olive recording sites. Arrow indicates a lesion (+50 μA, 10 s) in the magnocellular red nucleus (RNm) corresponding to the location of the caudal stimulating electrode of a bipolar pair. Cells in the RNm have been marked with filled circles. The calibration bars are 2 mm in both A and B. rMAO, rostral medial accessory olive.
evoked potential from the VF following stimulation of the hindlimb. The time of hindlimb shock corresponds to the beginning of the trace, and the evoked response began 6 ms after stimulation. Stimulation via the VF electrodes evoked a response in rDAO (Fig. 3C) with a latency of ~12 ms. Conditioning stimulation of the RNm before the VF stimulus eliminated the rDAO evoked response (Fig. 3D), thereby indicating that RNm stimulation produces inhibition within rDAO.

The sum of the hindlimb (hl) to VF and VF to rDAO latencies is 18 ms, which is close to the hl to rDAO latency of 19 ms. Therefore, it is likely that the fastest conducting fibers in the VF provide a strong input to rDAO [also, sectioning of the dorsal column (DC) did not increase rDAO response latency to foot shock].

To gain a more representative measure than given by single traces, recordings were rectified (which reduces cancellations introduced by phase shifts between trials) (see Horn et al. 1996a), integrated (1-ms time constant), and averaged (20 trials). Figure 4A illustrates the averaged evoked potential from the VF recordings; the record shows a rapid increase in amplitude 6 ms after hindlimb foot shock. Figure 4B illustrates evoked responses from hindlimb rDAO to VF stimulation. Traces with (-----) and without (---) prior conditioning stimulation of RNm are illustrated. As was the case for the individual records, the averaged rDAO response had an abrupt onset with a 13-ms latency and, except for a small early component (possibly, a presynaptic response), was strongly reduced by RNm conditioning stimulation.

VF stimulation was used to excite hindlimb rDAO in two preparations, and both showed strong response inhibition after RNm conditioning. In one preparation, inhibition was tested both before and after a bilateral section through the dorsal columns and dorsolateral funiculi immediately rostral to the VF stimulation site, to provide further assurance that the VF stimulation was exciting the olive only by activation of VF pathways. After the section, stimulation of either the VF or hindfoot elicited a strong evoked response in hindlimb rDAO, and both responses were inhibited by RNm conditioning stimulation.

In three other experiments, the dorsal half of the cord was sectioned at T12, and rDAO was tested for RNm-mediated inhibition using hindlimb shock as a stimulus. In all cases, RNm stimulation inhibited rDAO-evoked responses to the hindlimb shock. Presumably, the inhibited input was traveling via the VF, and possible inhibition occurring at lower spinal levels would have been eliminated by the T12 dorsal section.

INHIBITION OF RESPONSES TO DC STIMULATION. The DC pathway to hindlimb rDAO relays through the gracile nucleus, so if RNm stimulation inhibits rDAO responses to DC stimulation, the locus of inhibition would be limited to either the gracile nucleus or rDAO, or, perhaps, both nuclei. As in the case for VF stimulation, a hindlimb area of rDAO was identified, and Fig. 3E illustrates the olivary evoked response to shock of the contralateral hindlimb. Figure 3F illustrates the evoked potential recorded from the surface of the DC at T12 following hindlimb shock. Figure 3G illustrates the evoked potential from hindlimb rDAO to bipolar surface stimulation of the DC, which was inhibited by RNm conditioning stimulation (Fig. 3H).

Figure 4, C and D, illustrates the rectified, integrated, and averaged (n = 20) record of the DC response to hl stimulation as well as rDAO responses to DC stimulation with and
without RNm conditioning. The averaged responses confirm that RNm conditioning inhibited rDAO responding to DC stimulation, thereby indicating that inhibition occurred at the level of the rDAO and/or gracile nucleus. Similar results were obtained from three experimental preparations.

The sum of the hl to DC latency (4.4 ms) and DC to rDAO latency (18 ms) is slightly longer than the latency of hl to rDAO (21 ms) for the traces illustrated in Fig. 3, E–G, but the latencies of rDAO responses to DC stimulation were often anomalously long. In the averaged record (Fig. 4D), the latency of the peak rDAO response to DC stimulation is almost as long as the latency of the rDAO response to hindlimb stimulation (Fig. 5C), which leaves no time for conduction from the hindlimb to T12. It is likely that the fastest DC fibers do not provide a strong input to rDAO (see later and Fig. 6, C and D), but additional experiments would be needed to discriminate between several possible explanations for the long rDAO latency to DC stimulation.

Is RNm-mediated inhibition specific for olivary pathways?

EVOKED RESPONSES IN SPINAL CEREBELLAR PATHWAYS WITH AND WITHOUT RNm CONDITIONING. The previous experiments indicate that RNm-mediated inhibition occurs within the rDAO, but it is possible also that inhibition occurs at lower spinal levels. If so, afferent volleys in the cord should demonstrate reduced potentials following conditioning stimulation of RNm. Figure 5A illustrates the evoked response recorded from the VF to foot shock with (— — —) and without (− − −) prior conditioning stimulation of the RNm. The traces are essentially identical, indicating that RNm conditioning had little effect on spinal neurons relaying sensory information from foot shock via the VF. Responses in rDAO were recorded simultaneously with the responses in VF, and the records are shown in Fig. 5C. In contrast to the VF response, the rDAO response to foot shock was strongly inhibited by conditioning stimulation of RNm.

Figure 5B illustrates evoked potentials recorded at the surface of the DC following hindlimb stimulation. As was the case for the VF, the evoked response following conditioning (— — —) was essentially identical to the evoked response with no conditioning stimulation (− − −).

FIG. 4. Averaged records of evoked potentials. Average (n = 20) rectified-integrated (1-ms time constant) evoked potentials following peripheral and spinal cord stimulation from cat 6. A: VF activity following hindlimb stimulation. B: hindlimb rDAO responses to VF stimulation (40 μA, 0.5-ms pulse) with (— — —) and without (− − −) RNm conditioning stimulation. C: DC response at T12 to hindlimb stimulation. D: hindlimb rDAO responses to DC stimulation (1.2 μA, 0.5-ms pulse) with (— — —) and without (− − −) RNm conditioning stimulation. The vertical calibration bar is 0.3 mV for all panels except A, which is 0.05 mV, RNm conditioning (60 μA, 0.1 ms, 400 Hz, 100-ms train).

FIG. 5. Lack of inhibition at spinal levels. Average (n = 20) evoked potentials to hindlimb stimulation recorded with (— — —) and without (− − −) prior conditioning stimulation to RNm (60 μA, 0.1 ms, 400 Hz, 100-ms train) from cat 6. A: VF-evoked activity. B: DC-evoked activity. C: hindlimb rDAO-evoked activity. Only rDAO activity was inhibited by RNm conditioning stimulation.
FIG. 6. Lack of inhibition at thalamus. Average (n = 20) evoked potentials in response to limb stimulation for cat 7. In all records, responses to stimulation following RNM conditioning (75 µA, 0.2 ms, 300 Hz, 100-ms train) are shown as solid lines and responses without conditioning are shown as dashed lines. A: rDAO potentials to forelimb stimulation. B: ventralis posterior lateralis (VPL) potentials to forelimb stimulation. C: rDAO potentials to hindlimb stimulation. D: VPL potentials to hindlimb stimulation. For each limb, RNM conditioning stimulation reduced the evoked response in rDAO but had no effect on the response in VPL. Vertical calibration line is 0.6 mV for A–C and 0.1 mV for D.

somatosensory-evoked responses in VPL thalamus to be inhibited by conditioning stimulation to RNM. To test this hypothesis, peripherally evoked responses were recorded from forelimb and hindlimb areas of VPL thalamus with and without prior conditioning stimulation of RNM in one experiment. Figure 6A illustrates rDAO responses to forelimb shock with no conditioning of RNM (---) and with conditioning stimulation applied to RNM 50 ms before foot shock (---); the conditioning stimulation inhibited the rDAO response. Figure 6B illustrates responses from forelimb VPL thalamus using the same preparation and stimulation parameters as used for Fig. 6A. Notice that the evoked responses were essentially identical with (---) and without (---) conditioning stimulation of RNM. Similar plots are shown for hindlimb rDAO (Fig. 6C) and hindlimb VPL (Fig. 6D). Again, there is little or no difference between VPL responses with and without prior conditioning stimulation to RNM (the VPL evoked response was somewhat larger after RNM conditioning). Although the RNM conditioning inhibited rDAO responses, there was no inhibition of VPL responses.

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LATENCY OF rDAO INPUT. Figure 6 highlights another feature of input to the rDAO, namely the response in rDAO occurred at a considerably longer latency than the response in VPL thalamus, even though the pathway to VPL thalamus requires conduction over a longer distance. For hindlimb rDAO, the peak response was almost 10 ms slower than the peak response in VPL thalamus (compare Fig. 6, C with D). It is likely that most of the input to rDAO arises from neurons with relatively slow conduction velocities, but even the longer latency components in the VPL-evoked potential were not inhibited by RNM stimulation. The results suggest that RNM conditioning stimulation either inhibits afferent input exclusive to the rDAO or generates inhibition only within the rDAO.

Is RNM-mediated inhibition limb specific?

INHIBITION PRODUCED BY STIMULATION OF THE DORSOLATERAL FUNICULUS. Due to fibers of passage, it is not possible to stimulate forelimb or hindlimb neurons selectively at the level of the RNM. However, because most forelimb RNM neurons do not send axons beyond the cervical enlargement (Huisman et al. 1982; Robinson et al. 1987), stimulation of the dorsolateral funiculus (DLF) below the cervical enlargement would selectively activate axons of hindlimb RNM neurons. If RNM-mediated inhibition of rDAO is a generalized effect, then inhibition would be expected for both forelimb and hindlimb regions of rDAO, even though only cells projecting to lumbar cord are activated. If inhibition is limb specific, then stimulation of the RST at thoracic levels should inhibit responses in hindlimb regions of rDAO but not in forelimb regions.

Because stimulation of the DLF would affect regions of the cord caudal to the point of stimulation, the DLF was sectioned immediately caudal to the stimulus site at T12. Presumably, RNM neurons and their axon collaterals (as well as other neurons with axons traveling in the DLF) would be activated antidromically by the stimulation. Figure 7A illustrates the evoked response from forelimb rDAO to limb stimulation with (---) and without (---) prior conditioning of RNM. As illustrated previously, the evoked response was strongly attenuated by RNM stimulation. Figure 7B illustrates recordings from the same rDAO site with (---) and without (---) prior conditioning stimulation to the contralateral DLF at thoracic levels; DLF stimulation at T12 did not inhibit forelimb regions of rDAO.
FIG. 7. Limb specificity of inhibition. Conditioning stimulation applied to the dorsolateral funiculus (DLF) at T₁₂ inhibits hindlimb but not forelimb rDAO. Solid traces represent evoked potentials following conditioning stimulation, and dashed traces are records without conditioning stimulation. Each trace is the average of 20 trials. A: evoked responses from forelimb rDAO; conditioning stimulation applied to RNm (50 μA, 0.2 ms, 300 Hz, 100-ms train). B: evoked responses from forelimb rDAO; conditioning stimulation applied to DLF at spinal level T₁₂ (75 μA, 0.2 ms, 300 Hz, 100-ms train). C: evoked responses in hindlimb rDAO; RNm conditioning stimulation. D: evoked responses in hindlimb rDAO; DLF conditioning stimulation. Vertical calibration bar is 0.4 mV for A and B and 0.3 mV for C and D. Records from cat 2.

Figure 7C illustrates the evoked response in rDAO to hindlimb stimulation in the same preparation as used for Fig. 7, A and B. The large early response was inhibited by prior RNm conditioning stimulation. Figure 7D illustrates recordings from the same site as used for Fig. 7C with (——) and without (−−−) conditioning stimulation to the DLF. The early component of the evoked potential was inhibited, just as it was with RNm stimulation. Stimulation of the DLF at thoracic levels, which antidromically activated rubrospinal and corticospinal neurons projecting to lower spinal levels, inhibited neurons in hindlimb but not forelimb rDAO. DLF conditioning stimulation was used in two experiments, and the same pattern of results was obtained in both cases.

DISCUSSION

Conditioning stimulation applied to either the RNm or RST shortly before presentation of a peripheral stimulus inhibits rDAO responses to the peripheral stimulation (Weiss et al. 1990); the present results extend this finding by demonstrating that some, perhaps all, of the inhibition occurs within rDAO. The pathway or pathways responsible for RNm-mediated inhibition are not known. The findings of Weiss et al. (1990) demonstrate that sectioning the contralateral RST at the level of the RNm eliminates inhibitory effects of RNm stimulation, whereas stimulation of the RST caudal to the section produces inhibition. Therefore it is likely that fibers traveling with the RST or collaterals of RST fibers terminate on cells that are inhibitory to rDAO.

The inferior olive receives input from cells in the dorsal column nuclei that are distinct from cells projecting to thalamus (Berkley et al. 1986; McCurdy et al. 1998), and collaterals from the RST terminate heavily among these cells (McCurdy et al. 1992). It is possible that some of the cuneate cells projecting to rDAO are inhibitory (Nelson and Mugnaini 1989), and their activation by RST stimulation produces inhibition within rDAO.

The deep cerebellar nuclei provide a major source of inhibitory input to the olive. Nucleo-olivary cells are small in size (Tolbert et al. 1976) and GABAergic (Angaut and Sotelo 1989, 1991), and activation of interpositus strongly inhibits rDAO responses to peripheral stimulation (Horn et al. 1996b). RNm stimulation could activate nucleo-olivary cells via RST terminations on cells in the lateral reticular nucleus (Robinson et al. 1987) that project to interpositus, or possibly via antidromic activation of interpositus cells that have collateral input to nucleo-olivary cells. However, ablation of the deep cerebellar nuclei does not eliminate RST-mediated inhibition of the contralateral rDAO (Weiss et al. 1990), so it is unlikely that all of the inhibition is mediated via this pathway.

Our findings that activation of hindlimb RST fibers selectively inhibits responses of hindlimb rDAO neurons and that thalamic and afferent pathway potentials are not attenuated by RNm conditioning stimulation suggests that inhibition is specific for the olive and is not a generalized effect on sensory pathways. Other experiments, however, have demonstrated that RNm stimulation inhibits sensory responses of cells in the trigeminal nucleus (Davis and Dostrovsky 1986), cuneate nucleus (Gray and Dostrovsky 1983), and the dorsal horn of the spinal cord (Gray and Dostrovsky 1984). Inhibition at spinal levels should be evident as reduced evoked potentials in the DC and VF, and inhibition in the cuneate should be evident as a reduction in evoked potential in forelimb regions of thalamus, yet we found no reduction in these potentials.

The most likely explanation for the discrepant findings lies in methodology. In our study, the levels for peripheral stimulation were set to elicit a near-maximal evoked re-
response from the rDAO. In the other studies, peripheral stimulation strengths were set at just suprathreshold levels to detect even slight inhibitory effects. RNm conditioning stimulation probably has weak inhibitory effects on responses of various sensory pathways but strong inhibitory effects on responses of rDAO neurons.

Inhibition of rDAO, however, may not be due entirely to inhibition within the olive, because it is possible that pre-olivary cells are selectively inhibited. The shorter latency evoked response in thalamus as opposed to rDAO (despite a longer pathway) indicates that rDAO receives a selective set of afferents. However, we detected no reduction in early or late components of the DC, VF, or thalamic evoked potentials due to RNm stimulation, so if preolivary neurons are inhibited, their fibers must contribute only a small component to these evoked potentials. It seems likely that the majority of RNm-mediated inhibition is occurring within the rDAO, although it is possible that olivary projecting neurons in the dorsal column nuclei are also inhibited.

Stimulation of motor cortex inhibits sensory responses of both climbing fibers (Leicht et al. 1973) and cuneate neurons (Towe and Jabbur 1961). Inhibition is maximal 30–70 ms following the cortical conditioning train, which is similar in time course to the inhibition seen in rDAO following RNm stimulation. Olivary inhibition produced by stimulation of motor cortex may involve the same pathways as inhibition produced by stimulation of RNm, because collaterals of corticospinal fibers terminate in the same cuneate and spinal regions as do collaterals of the RST (McCurdy et al. 1992).

The delayed time course of olivary inhibition (Weiss et al. 1990) suggests that the neural mechanism for inhibition is not direct. One possibility is that there exists a two-neuron inhibitory pathway, with the second neuron, which projects to the olive, exhibiting rebound excitation following cessation of the conditioning train. Another possibility is that there are more or less balanced excitatory and inhibitory inputs during stimulation, but the inhibitory input has a longer time course of decay so that inhibition dominates on cessation of stimulation. The latter possibility is supported by the finding that motor cortical stimulation produces both excitatory postsynaptic potentials and inhibitory postsynaptic potentials in olivary neurons (Crill 1970).

**rDAO sensitivity during movement**

Studies of olivary sensitivity in the awake cat support the hypothesis that activity in motor pathways strongly inhibits olivary responding. When cats reach, grasp, and hold a lever, neurons in rDAO are essentially insensitive to sensory stimuli during the entire behavior, but they are sensitive during periods of stance between trials (Horn et al. 1996a). The reaching to grasp behavior results in high rates of discharge in RNm (Horn et al. 1992) and interpositus (Van Kan et al. 1994), and it is likely that this activity produces inhibition within rDAO.

Several studies have estimated olivary sensitivity by measuring the amplitudes of cerebellar climbing fiber field potentials in response to nerve stimulation (Apps et al. 1990). During locomotion the potential shows modulation dependent on the time of stimulation in relation to the step cycle. Typically, modulation is in a downward direction, although some evidence for an enhancement of sensitivity at specific times in the cycle exists (Apps et al. 1995). Our present study revealed no instances of enhanced sensitivity following RNm conditioning stimulation, but there may be both excitation and inhibition occurring during the train. If so, activity in motor pathways during behavior might produce periods of heightened olivary sensitivity. However, during reaching the rDAO and climbing fiber responses appear to be strongly inhibited through all phases of the behavior (Apps et al. 1997; Horn et al. 1996a).

Apps et al. (1997) conclude that inhibition during reaching is preolivary because spontaneous discharge in rDAO is not inhibited during reaching (Horn et al. 1996a), but we found no evidence for inhibition at preolivary levels. Most spino-olivary fibers terminate on distal dendrites of rDAO neurons (Molinari 1988); if the synaptic inputs responsible for the observed inhibition are located at these distal sites, they could exert a strong inhibition of spino-olivary input while having little effect on excitatory events at the soma. It is also possible that the inhibition is presynaptic, which would have little affect on spontaneous discharge.

Several studies have reported movement-related inhibition in afferent pathways at preolivary levels. Evoked potentials from the cat medial lemniscus are reduced by 10–40% during active movement (Chapman et al. 1988; Coulter 1974; Ghez and Pisa 1972). However, during a reach-to-grasp, cuneate neurons maintain sensitivity to somatosensory stimulation and respond well to stimulation resulting from movement (Horn et al. 1997). It is likely that additional inhibition is specific to the rDAO and/or to dorsal column neurons that provide input to rDAO.

**Functional considerations**

Why is it important to prevent the inferior olive from discharging during movement? When an olivary cell discharges, the resulting complex spike in the Purkinje cell produces a loss of simple spikes for ~40–60 ms. Repetitive complex spike discharge, even at low rates, can completely inhibit simple spike discharge (Rawson and Tilokskulchai 1981). It is unlikely that a Purkinje cell contributes significantly to the control of movement in the absence of simple spikes, and, therefore, high olivary sensitivity during movement might actually be disruptive if there were movement-induced complex spikes. Olivary inhibition during movement might prevent such disruption.

The previous explanation might explain why it is desirable to have low olivary sensitivity during movement but does not explain why olivary sensitivity is high in the absence of movement. rDAO neurons have well-defined receptive fields (Gellman et al. 1983), so the discharge of a given neuron signals that a particular place on the body has been touched. The precise anatomic relationship between the inferior olive and cerebellum (Groenewegen et al. 1979) indicates that the discharge of a particular rDAO neuron ultimately influences areas of cerebellum concerned with moving the particular part of the body that has been touched (Ekerot et al. 1995; Gibson et al. 1987).

It might seem logical that the olive would play a role in the initiation of movement in some sort of cerebellar reflex, but the olivocerebellar pathways are slow, and stimulation
within the olive does not trigger movement (Gellman et al. 1985; Gibson and Chen 1988). Therefore it seems more likely that olivary discharge modulates the state of specific cerebellar areas, and several theories of olivary function postulate such action.

Although high rates of climbing fiber discharge can completely inhibit simple spikes, low rates of discharge may have a very different effect on simple spikes: Ebner and Bloedel (1981) reported an enhancement in Purkinje cell sensitivity to peripheral input for a period of time following a complex spike and suggest that olivary discharge may help determine the pattern of activation produced by mossy fiber inputs to cerebellar cortex. Peripheral stimulation might cause synchronous discharge in a given parasagittal zone, so that the affected zone is sensitized to mossy fiber inputs (Bloedel 1992) and, thus, contributes more importantly to cerebellar output.

Another possibility is that pairing of mossy and climbing fiber activity leads to long-term changes in Purkinje cell responses to mossy fiber inputs (Ito et al. 1982), and there is evidence that the olive might signal the occurrence of the unconditioned stimulus (UCS) in a classical conditioning paradigm (Mauk et al. 1986; Sears and Steinmetz 1991). The hypothesis fits well with the predominantly somatosensory nature of olivary input, but the current results as well as other findings (Horn et al. 1996a) indicate that the olive is inhibited during movement. Therefore one would expect that classical conditioning would be relatively ineffective during movement, because olivary inhibition would prevent signaling of the UCS.

Although function of the inferior olive remains highly speculative, there is little question that sensory responses of olivary neurons are inhibited during movement. The results from the present study demonstrate that a large amount of inhibition generated by activity in a descending motor pathway is intrinsic to the olive: inhibition by motor pathways is likely to be a salient feature of olivary function.

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