Exp Brain Res (1993) 94:203–215

Experimental Brain Research

Activity of neurons in the beta nucleus of the inferior olive of the rabbit evoked by natural vestibular stimulation

N.H. Barmack[1], M. Fagerson[1,2], B.J. Fredette[3], E. Mugnaini[3], H. Shojaku[1,4]

[1] R.S. Dow Neurological Sciences Institute, Good Samaritan Hospital and Medical Center, Portland, Oregon, USA
[2] Department of Cell Biology and Anatomy, Oregon Health Sciences University, Portland, Oregon, USA
[3] Laboratory of Neuromorphology, Psychology-Behavioral Neuroscience, University of Connecticut, Storrs, Connecticut, USA
[4] Department of Otolaryngology, Toyama Medical and Pharmaceutical University, Toyama, Japan

Received: 16 April 1992 / Accepted: 12 February 1993

Abstract. The inferior olive (IO) appears to be organized functionally in discrete subnuclei that receive transmitter-specific inputs. In particular, the IO receives a GABAergic input that is most densely concentrated in the β-nucleus. In this experiment, we examined the functional specificity of neurons in the β-nucleus of the IO of rabbits by recording their activity during natural vestibular and optokinetic stimulation. Rabbits were anesthetized and positioned in a triaxial servo- controlled rate table with the head fixed at the center of rotation. Contour-rich visual stimuli were rear-projected onto a 70 deg tangent screen and moved at constant velocities. Recording sites in the β-nucleus were verified by subsequent histological analysis of marking microlesions. Neurons in the β-nucleus responded to roll vestibular stimulation about the longitudinal axis. These neurons were excited when the rabbit was rolled onto the side which was contralateral to the recording site, and inhibited when the rabbit was rolled ipsilaterally. Thirty-eight of the 75 β-nucleus neurons that were responsive to roll vestibular stimulation also responded to static tilt, indicating an otolithic as well as a vertical semicircular canal origin of the vestibular input. The modulated activity of none of the neurons could be attributed to stimulation of the horizontal semicircular canals. All the recorded neurons were found in a region of the β-nucleus that was retrogradely labeled following HRP injections into the cerebellar nodulus. Using a "null point" technique, we found that there was a differential projection of information from the anterior and posterior semicircular canals onto to the β-nucleus. Stimulation of the ipsilateral anterior–contralateral posterior semicircular canals modulates activity of the neurons in the caudal 500 μm of the β-nucleus. Stimulation of the ipsilateral posterior–contralateral anterior semicircular canals modulates activity of neurons located more rostrally. β-nucleus neurons and the olivocerebellar circuits in which they participate may constitute an important pathway for the control and adaptive modification of postural reflexes.

Key words: Cerebellum – HRP – Single unit recording – Vestibular stimulation – Rabbit

Correspondence to: N.H. Barmack, R.S. Dow Neurological Sciences Institute, 1120 N.W. 20th Avenue, Portland, OR 97209, USA

Introduction

The inferior olivary (IO) complex, the exclusive source of climbing fibers to the cerebellum, receives inputs from at least three sensory systems; visual (Maekawa and Simpson 1973; Alley et al. 1975; Frankfurter et al. 1976; Weber et al. 1978; Maekawa and Takeda 1979; Takeda and Maekawa 1980; Saint-Cyr and Courville 1982; Kawamura and Onodera 1984; Leonard et al. 1988; Kyuhou and Matsuzaki 1991), vestibular (Walberg 1974; Saint-Cyr and Courville 1979) and somatosensory (Martin et al. 1975; Berkley and Hand 1978a; Berkley and Hand 1978b; Gellman et al. 1983; Huerta et al. 1985; Molinari et al. 1991). These inputs appear to terminate in very specific regions of the IO that are topographically restricted. For example, the dorsal cap of the IO is innervated by one class of visual input that originates from the ipsilateral accessory optic system as well as the ipsilateral nucleus of the optic tract. Neurons in the dorsal cap of Kooy (Kooy 1916) have been characterized physiologically as directionally-selective and velocity-sensitive to large field, contour-rich optokinetic stimulation (Maekawa and Simpson 1973; Alley et al. 1975; Maekawa and Takeda 1979; Takeda and Maekawa 1980; Kawamura and Onodera 1984; Leonard et al. 1988). These optokinetically driven neurons appear to be organized in a visual coordinate system that is approximately congruent with the axes of rotation of the semicircular canals. Neurons responding to optokinetic stimulation in the horizontal plane appear to be located in the caudal half of the dorsal cap (Fig. 1). Neurons responding to optokinetic stimulation in the planes of the vertical semicircular canals are located more rostrally, closer to the

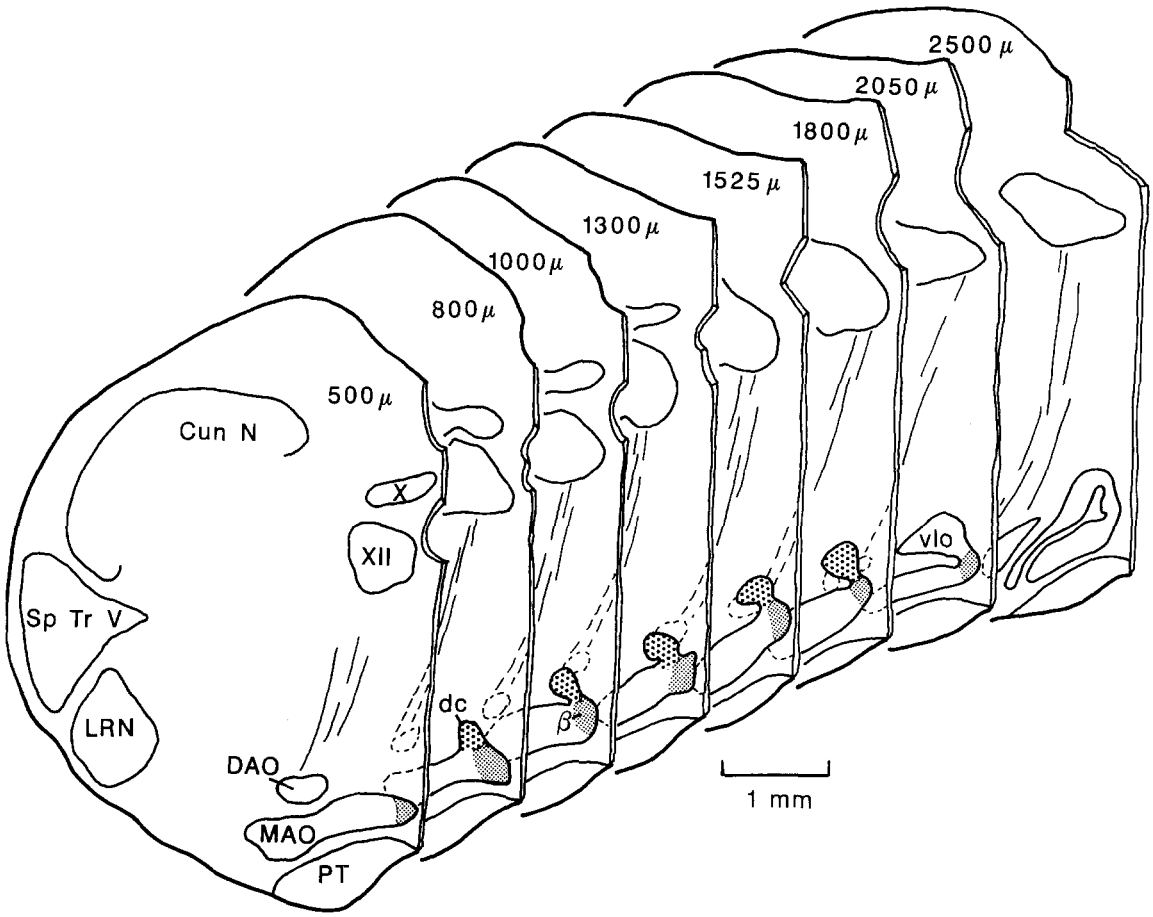


Fig. 1. Illustration of the rostro-caudal extent of the β-nucleus, dorsal cap and medial accessory olive in the rabbit. The caudal half of the IO is illustrated. The β-nucleus is indicated by *smaller stippling*. The dorsal cap is identified by *larger stippling*. β, β-nucleus; *Cun N*, cuneate nucleus; *DAO*, *MAO*, dorsal and medial accessory olive; *dc*, dorsal cap of Kooy; *LRN*, lateral reticular nucleus; *PT*, pyramidal tract; *Sp Tr V*, spinal trigeminal nucleus; *vlo*, ventral lateral outgrowth; *X*, dorsal motor nucleus of the vagus nerve; *XII*, hypoglossal nucleus

ventrolateral outgrowth (Leonard et al. 1988). A second visually related input to the IO, less well characterized physiologically, originates from the contralateral superior colliculus and terminates within the caudal third of the medial accessory olive just ventral to the β-nucleus (Frankfurter et al. 1976; Weber et al. 1978; Saint-Cyr and Courville 1982; Kyuhou and Matsuzaki 1991).

A third pathway that may carry visual, vestibular or eye movement related information to the dorsal cap originates primarily from the contralateral nucleus prepositus hypoglossi (NPH) (Gerrits et al. 1985; McCrea and Baker 1985; Barmack et al. 1993b; De Zeeuw et al. 1993). Recently, it has been shown that the NPH projection to the dorsal cap of the rabbit is primarily contralateral and that it is, at least in part, GABAergic (De Zeeuw et al. 1993). In the rat, the projection to the dorsal cap from the NPH is primarily, but not exclusively, cholinergic (Barmack et al. 1993b).

Vestibular inputs to the IO arise from the medial and descending vestibular nuclei (MVN, DVN). These vestibular pathways terminate within the ipsilateral β-nucleus (Walberg 1974; Saint-Cyr and Courville 1979) and in both the ipsilateral and contralateral dorsal medial cell column (Saint-Cyr and Courville 1979). Immunohistochemical investigations have demonstrated that the vestibular input to the β-nucleus is GABAergic (Nelson et al. 1986; Nelson et al. 1989; Fredette and Mugnaini 1991).

A previous attempt to determine the characteristics of vestibularly driven simple spikes (SSs) and climbing fiber responses (CFRs) at the level of the cerebellar Purkinje cells located in the uvula-nodulus ended with the conclusion that natural modulation of both types of responses occurs during sinusoidal stimulation in the horizontal plane (Precht et al. 1976). However, the CFRs evoked in Purkinje cells had relatively high thresholds and low sensitivities to horizontal angular acceleration. Similarly, another experiment in which the activity of inferior olivary neurons was evoked by sinusoidal, horizontal angular acceleration reported that roughly 20% of the neurons studied were weakly driven by the vestibular stimulus (Robinson et al. 1988). In neither of these two experiments were axes of vestibular stimulation other than the vertical (yaw) axis tested.

The present experiment was initiated with three aims: (1) to examine the vestibular-related activity of neurons located in the β-nucleus, a region that is known to receive a GABAergic secondary afferent vestibular projection,

(2) to determine which components of the peripheral vestibular apparatus contribute to vestibularly evoked olivary activity, and (3) to learn if there is a systematic parametric encoding of vestibular stimulation by olivary neurons.

Neurons located in the β-nucleus receive information from the vertical semicircular canals, as well as the utricular otoliths. In all instances, the responses of neurons recorded in the β-nucleus were of the "Type II" variety; an increase in activity was evoked by roll about the longitudinal axis onto the contralateral side. The polarity of the vestibularly evoked responses is consistent with the idea that these responses are conveyed to the β-nucleus by immunohistochemically demonstrated GABAergic pathway and that this input is functionally inhibitory. We could find no evidence for an input to neurons of the β-nucleus mediated by the horizontal semicircular canals. Finally, we have discovered a functional topographic projection of the vertical semicircular canals onto β-nucleus neurons. Neurons driven from the ipsilateral anterior–contralateral posterior semicircular canals are located posteriorly within the β-nucleus. Neurons driven from the ipsilateral posterior–contralateral anterior semicircular canals are represented more rostrally.

Materials and methods

Vestibular stimulation

Adult pigmented rabbits weighing 1.0–1.4 kg were anesthetized with intramuscular injections of ketamine hydrochloride (50 mg/kg), xylazine (6 mg/kg) and acepromazine maleate (1.2 mg/kg). The head of the rabbit was attached by implanted head bolts to a restraining bar which held the head and a microdrive rigidly in the center of rotation of a three-axis vestibular rate table, with the plane of the horizontal semicircular canals maintained in the earth horizontal plane. The body of the rabbit was encased in foam rubber and fixed with elastic straps to a semicircular plastic tube aligned with the longitudinal axis. The rate table was sinusoidally oscillated about the vertical axis (yaw), about the longitudinal axis (roll) or about the interaural axis (pitch) (±10 deg, 0.02–0.80 Hz). During vestibular stimulation the vision of the rabbit was always completely occluded.

In five experiments a "null technique" was used to determine the peripheral origin of vestibularly modulated activity in the β-nucleus. While the rabbit was rotated about the longitudinal axis, the angle of its head about the vertical axis was changed systematically until a minimum in the vestibularly modulated neuronal activity was detected, a "null point." On either side of this null point the phase of the vestibularly modulated activity was shifted with respect to the sinusoidal vestibular forcing function by 180 deg. For each tested neuron, the null point characterized the orientation of a particular pair of vertical semicircular canals, i.e., left anterior–right posterior or right anterior–left posterior semicircular canals, as being 90 deg from their optimal response planes.

A "static roll" test was used to determine whether the discharge of a β-nucleus neuron was related to otolithic stimulation. In this test, the rabbit was tilted 5–10 deg about the longitudinal axis. After an adaptation period of 30 s, the average discharge frequency was measured for the next 30 s. The static roll test was then repeated in the opposite direction. A difference in average discharge frequency of more than 20% for roll stimuli of two different directions was taken as evidence of an otolithic sensitivity to the linear acceleration of gravity.

Optokinetic stimulation

The rate table was located 55 cm from the center of a rear- projection tangent screen which subtended 70 × 70 deg of visual angle. An optokinetic stimulus was rear-projected onto the screen by beaming the image of a random dot contour-rich pattern, projected by a 35 mm slide projector, off three first surface mirrors, two of which were mounted orthogonally on EEG pen motors. Appropriate voltage ramps to the pen motors generated constant velocity movement of the projected image on the tangent screen in the horizontal and vertical axes.

Microelectrode recording

Tungsten microelectrodes or indium-filled glass pipettes were used to obtain extracellular single olivary neuron recordings. The electrode was advanced toward the β-nucleus after exposing the dorsal aspect of the brainstem, just rostral to the obex and caudal to the uvula-nodulus of the cerebellar vermis. Sometimes more than one neuron was recorded by the microelectrode. The signal from the microelectrode was amplified (bandwidth 0.1–10|000 Hz). A window discriminator was used to discriminate the action potential of a single neuron. The output of the window discriminator was connected to a DEC LSI 11/23 computer and the evoked activity was displayed online as peristimulus histograms. At the completion of an electrode track, one or more electrolytic marking lesions (3–10 μA) were made for 10 s at depths at which stimulus-driven olivary activity was found.

HRP histochemistry

In two adult pigmented rabbits, the pattern of projection of neurons of the β-nucleus to the posterior cerebellum was studied using the retrograde transport of horseradish peroxidase (HRP).The rabbits were anesthetized with intramuscular injections of ketamine hydrochloride (50 mg/kg), xylazine (6 mg/kg) and acepromazine maleate (1.2 mg/kg). Under aseptic surgical conditions, the caudal cerebellum was exposed and a 30% solution of HRP in 0.9% NaCl was pressure injected through a glass micropipette connected to a 1 μl syringe (Hamilton). The micropipette was inserted through the dorsal uvula into the ventral aspect of the uvula and into the nodulus, at several medial-lateral locations. A total of 0.5–2.0 μl of HRP was pressure injected. Following 2–3 day postoperative survival, the rabbits were deeply anesthetized with sodium pentobarbital (60 mg/kg). They were subsequently perfused transcardially with 0.9% NaCl, followed by a 1.0% paraformaldehyde and 1.25% glutaraldehyde in 0.1 M PBS, pH 7.4, lasting 20–30 min. The fixation was terminated with a rinse of 0.1 M PBS, pH 7.4. The brains were removed and cryoprotected with 10%, 20% and 30% sucrose in 0.1 M PBS, pH 7.4. The brainstem and cerebellum were cut into blocks, mounted onto cork with OCT compound, and frozen in isopentane cooled with liquid nitrogen. Frozen sections (30–40 μm) were cut and collected in cold 0.1 M PBS, pH 7.4. A DAB-stabilized, $CoCl_2$-intensified, tetramethylbenzidine (TMB) reaction (Rye et al. 1984; Olucha et al. 1985) was used to demonstrate the presence of retrogradely transported HRP as a granular black reaction product.

Results

Microelectrode recordings from single neurons in the β-nucleus

The microelectrode recordings from the β-nucleus gave unexpectedly uniform results. We recorded from a total of 94 neurons that were located within the β-nucleus on

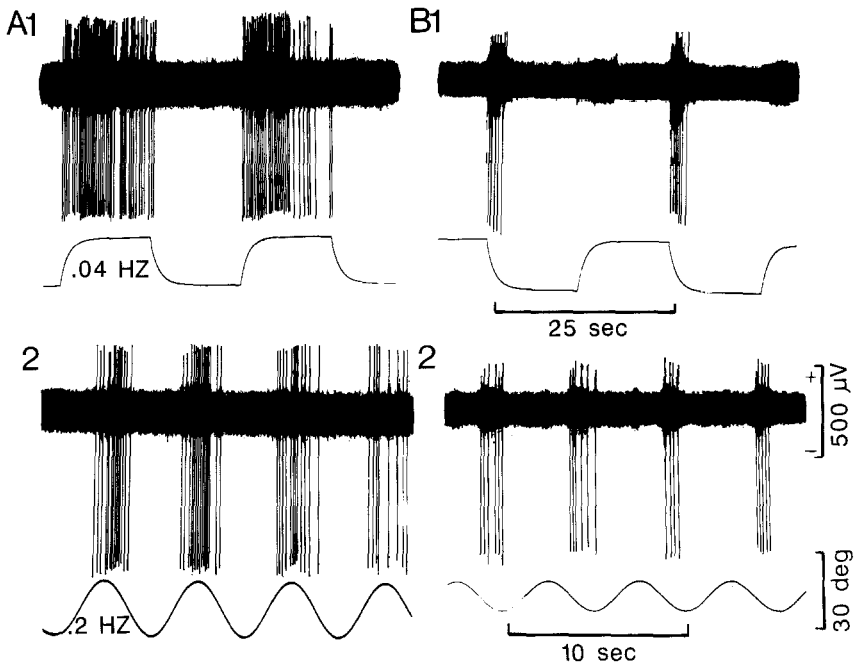


Fig. 2A,B. Vestibular-evoked responses for two β-nucleus neurons are illustrated in response to two types of vestibular stimulation. The neuron in the *left panels* was responsive to static tilt. The neuron in the *right panels* was not responsive to static tilt. In **A1**, **B1** the stimulus was a low frequency, 0.04 Hz, 20 deg, exponential "step" about the longitudinal axis (roll) with a time constant of 1.5 s. In **A2**, **B2** the stimulus was a sinusoidal roll about the longitudinal axis: **A2**, 0.20 Hz, ±10 deg, **B2**, 0.20 Hz, ±6.5 deg. *Upward deflections* of the stimulus traces indicated left side down. The cell in **A1,2** responded to left side down steps and responded in phase with left side down position, −80 deg with respect to velocity. The cell in **B1,2** responded transiently during steps onto the right side, and discharged with a phase of −15 deg with respect with head velocity.The cell illustrated in **A** was located in the right β-nucleus and the cell in **B** was located in the left β-nucleus

the basis of a direct marking lesion, or with respect to a known distance and depth of a recording track from a track in which a marking lesion was placed. Of this total, 75 of the neurons responded to roll vestibular stimulation about the longitudinal axis. The locations of 41 of these neurons within the β-nucleus was confirmed directly from marking lesions. Each of the neurons that responded to vestibular stimulation was excited when the rabbit was rolled onto the side contralateral to the recording site, and inhibited when the rabbit was rolled onto the ipsilateral side. This invariant relationship is illustrated for two cells in Fig. 2 for both "exponential step" and sinusoidal vestibular stimuli. The neuron illustrated in Fig. 2A was localized in the right β-nucleus. It responded to a vestibular step onto the left side with a discharge that slowly adapted. When stimulated sinusoidally about the longitudinal axis, this neuron fired in phase with the left side down position. The activity of this neuron was recorded during maintained steps, and by the criteria listed in Materials and methods had an otolithic component. By contrast, the neuron illustrated in Fig. 2B was localized in the left β-nucleus and discharged only transiently during vestibular steps onto the right side. It discharged in phase with rightward velocity.

The activity of another neuron isolated in the right β-nucleus was tested at 0.02 Hz (Fig. 3B), 0.05 Hz (Fig. 3C) and 0.2 Hz (Fig. 3D). The activity of this neuron was modulated by sinusoidal vestibular roll stimulation about the longitudinal axis. This neuron also responded to a static 5 deg roll onto the left side. We did not determine a "null point" for this neuron, nor did we test its visual sensitivity.

Comparison of stimulus specificity for β-nucleus neurons and dorsal cap neurons

Figure 4 illustrates the responses of two neurons which were recorded on successive electrode penetrations through the left IO. Fig. 4A1–3 show the responses of a neuron located within the dorsal cap. It was excited by posterior → anterior stimulation of the right eye and disfacilitated by anterior → posterior stimulation. The cell evinced transient increases in discharge frequency when the constant velocity optokinetic stimulus changed directions from anterior → posterior to posterior → anterior with respect to the viewing eye. Conversely, the discharge frequency decreased transiently when the optokinetic stimulus changed direction from posterior → anterior to the anterior → posterior. The cell was unresponsive to posterior → anterior stimulation of the *left* eye. Horizontal vestibular stimulation (yaw) at 0.10 Hz failed to modulate the activity of this neuron (Fig. 4A3). Roll vestibular stimulation (not illustrated) was also ineffective in modulating the activity of this dorsal cap neuron. Fig. 4B1–3 illustrates the stimulus-related activity of a neuron located in the left β-nucleus. The neuron was excited by vestibular roll stimulation onto the right side. The neuron responded in phase with rightward velocity. The activity of this neuron was not modulated by static tilt, nor was it modulated by horizontal vestibular stimulation (yaw). This β-nucleus neuron was also unresponsive to vertical optokinetic stimulation of the left eye. The right eye was not tested.

The phase of vestibularly-modulated discharge in β-nucleus neurons to head velocity

Of the 75 neurons that were responsive to roll vestibular stimulation, 38 were at least partially responsive to static roll, indicating an otolithic vestibular input to the β-nucleus. We measured the phase of the vestibularly evoked responses of neurons that were sensitive to static tilts, and compared the phases with a group of neurons that were not sensitive to static tilts. This comparison was made for all neurons in both groups for which phase measurements were made at a frequency of 0.1–0.2 Hz.

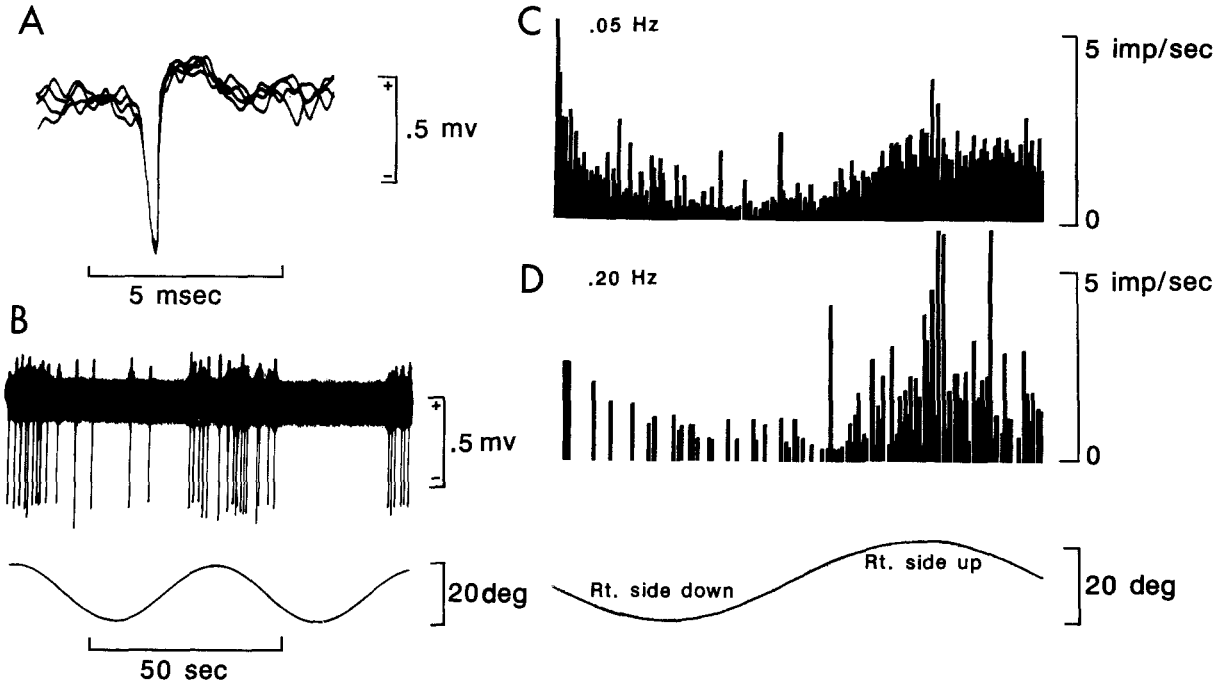


Fig. 3. **A** Four superimposed traces of the action potential of a β-nucleus neuron. **B** Activity evoked in the same neuron by sinusoidal vestibular stimulation about the longitudinal axis. The *lower trace* indicates the position of the head-body, rotated about the longitudinal axis. An *upward deflection* indicates right side up. The olivary neuron increased its activity when the rabbit was rotated onto its left side. **C, D** Peristimulus time histograms of the activity evoked in the same olivary neuron at two different frequencies of stimulation, 0.05 and 0.20 Hz, about the longitudinal axis. Each bin corresponds to 2 deg. In **C** and **D**, the peristimulus histograms consist of 40 cycles of vestibular stimulation

The mean phase for the group of β-nucleus neurons that responded to static tilt was -74 ± 20 deg ($n=15$) with respect to head velocity. The mean phase with respect to head velocity for the group of β-nucleus neurons that did not respond to static tilt was -34 ± 27 deg ($n=25$).

Distribution of vestibularly modulated neurons of the β-nucleus

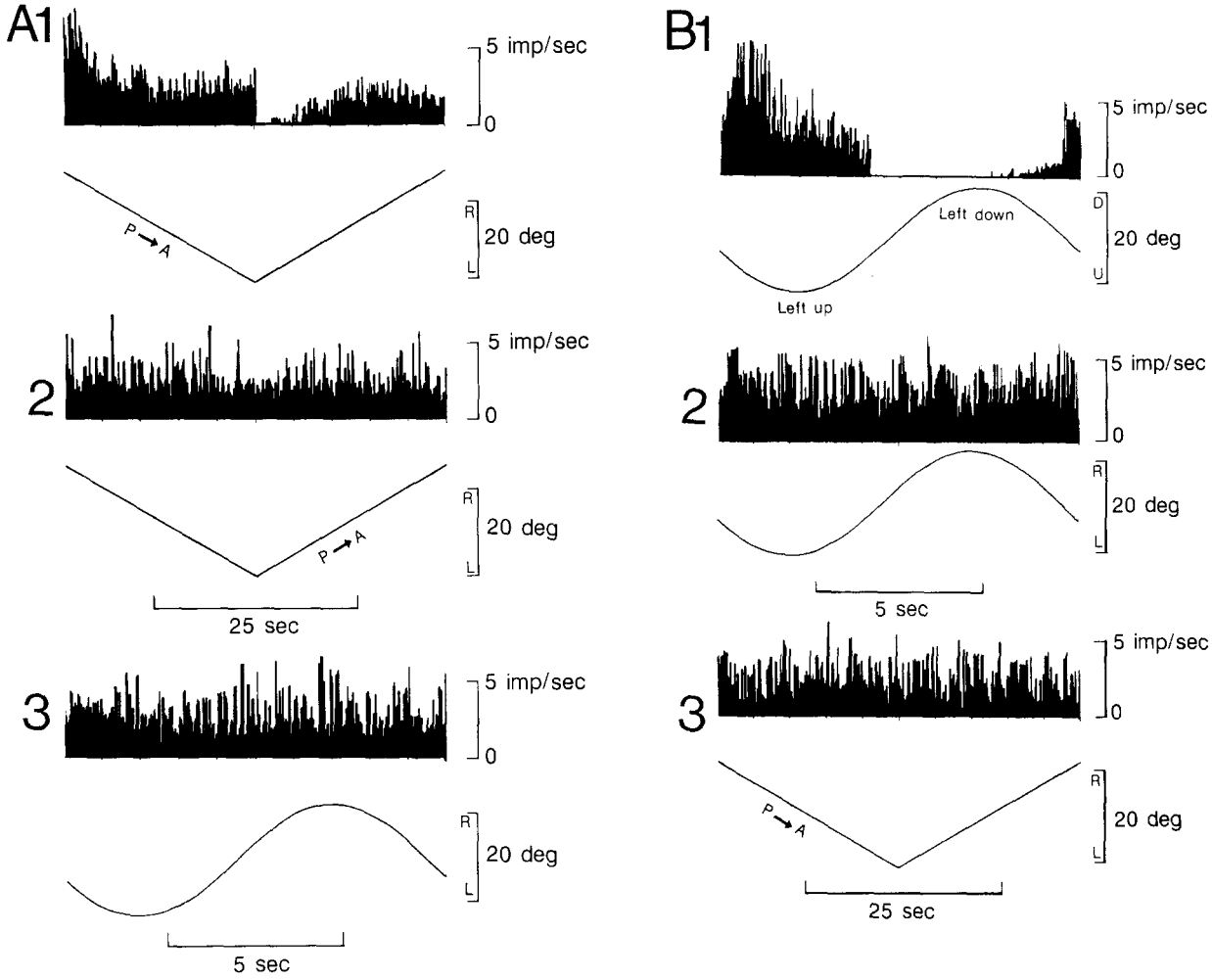
We made a map of 23 neurons that were both vestibularly driven, which we were able to recover electrolytic marking lesions, and for which we did not try to obtain information concerning the null point of vestibularly-evoked discharge. These neurons were located in the β-nucleus and were distributed from its most caudal origin (Fig. 5B6) to just caudal to the ventrolateral outgrowth (Fig. 5B1). The location of these vestibularly responsive neurons was coextensive with the neurons in the β-nucleus that were retrogradely labeled following an HRP injection into the uvula-nodulus (Fig. 5). Other vestibularly driven neurons were found outside the β-nucleus, along the midline as the microelectrode was advanced towards the β-nucleus. These extra-olivary neurons will not be further considered in this report.

Null point testing of neurons in the β-nucleus

In five rabbits, we recorded from 15 neurons that were localized to the β-nucleus and for which we were able to obtain null point measurements. We varied the angle of the head of the rabbit about the vertical axis while rotating the rabbit about the longitudinal axis (see Materials and methods). Null points were measured at stimulus frequencies of 0.2–0.4 Hz.

Fig. 6A–D illustrates the application of these testing procedures to the analysis of the vestibularly evoked activity of two simultaneously recorded neurons in the right β-nucleus. The activity of the neuron with the larger action potential was modulated by roll vestibular stimulation delivered about the longitudinal axis (Fig. 6A,F). Again, when the rabbit was rolled onto its right side the evoked-activity decreased, and when the rabbit was rolled onto its left side the activity increased. The longitudinal axis of the head was then rotated clockwise (viewed from above) until the vestibularly evoked activity was phase shifted by 180 deg with respect to the sinusoidal roll stimulus. This occurred when the head-body axis was rotated clockwise by 48 deg (Fig. 6B). The null point corresponded to 45 deg, the angle at which there was no clear relation of the activity of the olivary unit and the sinusoidal roll stimulus. This "null point" corresponded to the angle at which the planes of the right posterior–left anterior semicircular canals were parallel to the longitudinal rotation axis.

The activity of the two neurons illustrated in Fig. 6 was also modulated by vestibular stimulation about the vertical axis (yaw) (Fig. 6C).However, this yaw-related activity could be attributed to an inappropriate alignment of the head of the rabbit with respect to the vestibular stimulus. When the horizontal vestibular stimulus



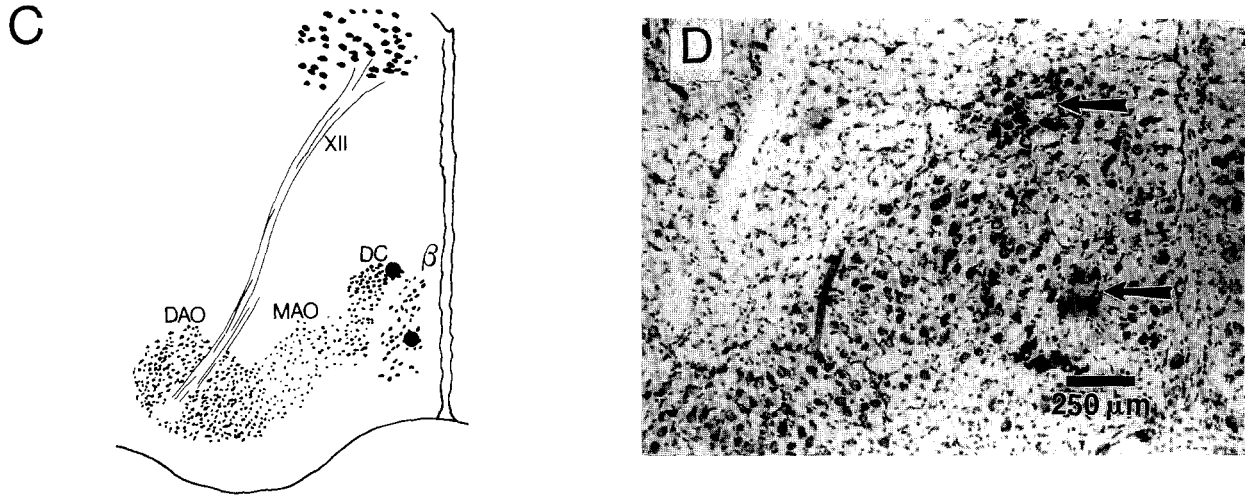


Fig. 4A–D. Comparison of the visual and vestibular responsiveness of a neuron located in the left caudal dorsal cap and a neuron located in the left β-nucleus.The panels on the *left* illustrate the activity of a dorsal cap neuron. **A1** Posterior→anterior optokinetic stimulation (1.2 deg/s) of the right eye evoked an increase in activity of a neuron in the left dorsal cap. **A2** Posterior→anterior stimulation of the ipsilateral (left) eye did not alter the neuronal activity. **A3** Horizontal vestibular stimulation at 0.1 Hz also did not alter the activity of the dorsal cap neuron. The *right panels* illustrate vestibularly evoked activity of a neuron located in the left caudal β-nucleus. **B1** Vestibular stimulation at 0.1 Hz about the longitudinal axis modulated the activity of this left caudal β-nucleus neuron. When the rabbit was rotated onto its right side, an increase in the activity of the olivary neuron was evoked in phase with velocity. **B2** Horizontal vestibular stimulation did not modulate the activity of this neuron. **B3** Vertical optokinetic stimulation of the right eye at 1.2 deg/s also did not modulate the activity of this neuron. The bin width of each peristimulus histogram corresponds to 2 deg. For peristimulus histograms **A1,2** and **B3** 20 stimulus cycles were averaged. For peristimulus histograms **A3** and **B1,2**, 80 stimulus cycles were averaged. The location of the recording sites of the two neurons is illustrated in **C**. The marking lesions are indicated by filled circles. **D** A photomicrograph shows the electrode locations in the dorsal cap and β-nucleus. The marking lesions are indicated by the *two arrows*. β, β-nucleus; *DAO*, dorsal accessory olive; *DC*, dorsal cap; *MAO*, medial accessory olive; *XII*, hypoglossal nerve

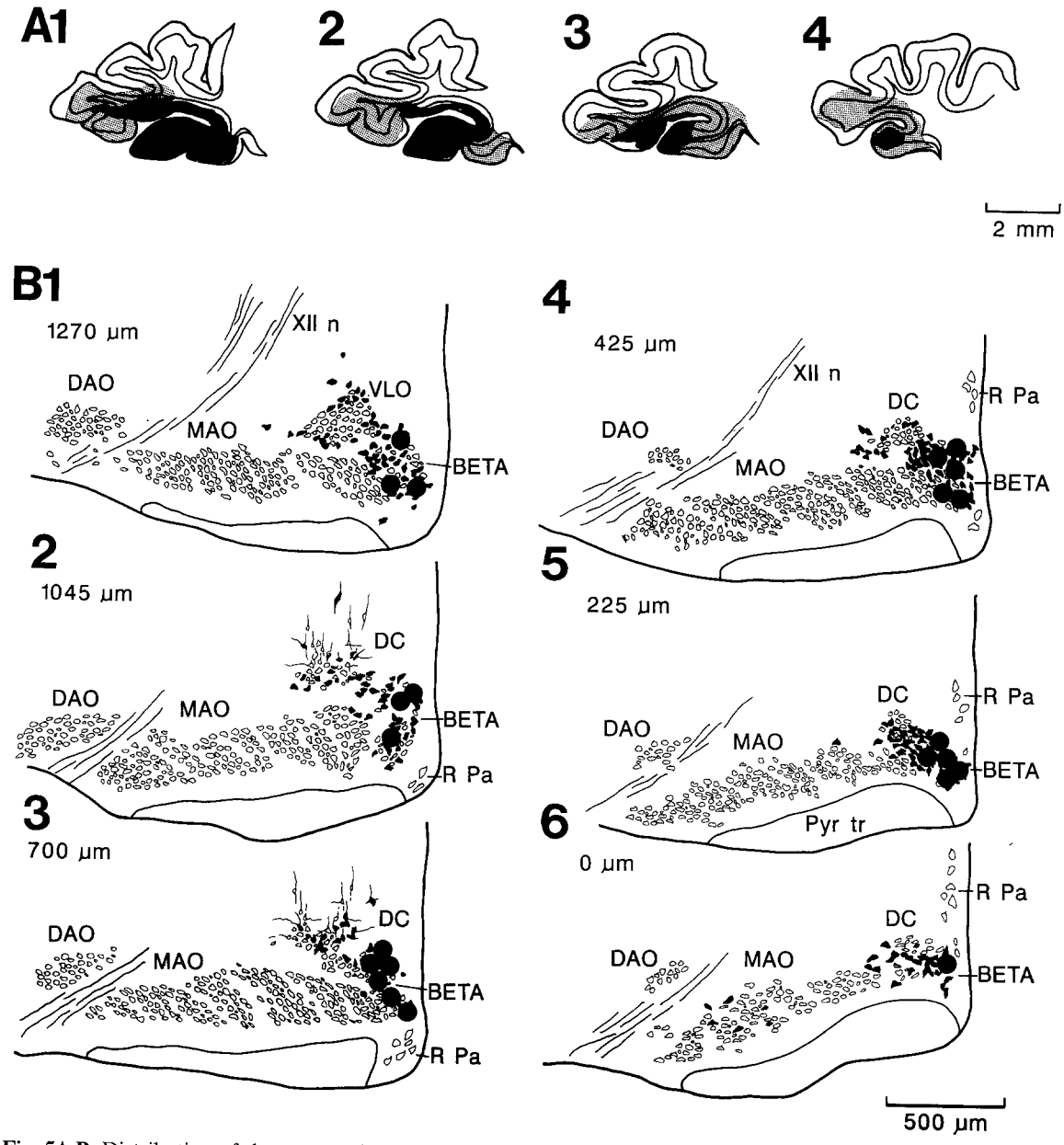


Fig. 5A,B. Distribution of the retrogradely labeled neurons in the β-nucleus following HRP injection into the nodulus and distribution of neurons in the β-nucleus from which neuronal activity was recorded. **A1–4** Illustration of sagittal sections, from medial to lateral, of the cerebellum of a rabbit that received multiple HRP injections in the right uvula-nodulus. The *dark areas* indicate the focal points of the injections and the *shaded areas* indicate areas into which HRP diffused. The sections are spaced approximately 425 µm apart. **B1–6** Illustration of transverse sections through the dorsal cap of the IO, from its most rostral extent B1 to its most caudal extent B6. The sections are spaced approximately 250 µm apart. The olivary cells that were filled retrogradely from the HRP injection illustrated in **A** are indicated in *black*. Neurons from which electrophysiological recordings were obtained *and* that were electrolytically marked are shown as *larger filled circles* in the map of the IO. Abbreviations: *BETA*, β-nucleus; *DAO*, dorsal accessory olive; *DC*, dorsal cap; *MAO*, medial accessory olive; *Pyr tr*, pyramidal tract; *R Pa*, raphe pallidus nucleus; *XII n*, hypoglossal nerve

was delivered with the rabbit tilted slightly (18 deg) onto its left side, the vestibularly modulated activity was not evoked (Fig. 6D). If the yaw-related activity originated from stimulation of the horizontal semicircular canals, tilting the rabbit slightly onto its left side would not cause the yaw-evoked activity to disappear.

Vertical optokinetic stimulation of the left eye was also capable of modulating the activity of the two β-nucleus neurons illustrated in Fig. 6E. An increase in activity was evoked by optokinetic stimulation in the downward direction with respect to the left eye. A peristimulus histogram of the neuron with the larger action potential is illustrated in Fig. 6G. Unlike the modulation in neuronal activity evoked by horizontal optokinetic stimulation of neurons in the dorsal cap (Fig. 4A), optokinetic modulation in activity of β-nucleus neurons did not cause transient increases in discharge frequency for one direction and transient decreases in discharge frequency for the opposite direction (Fig. 6G).

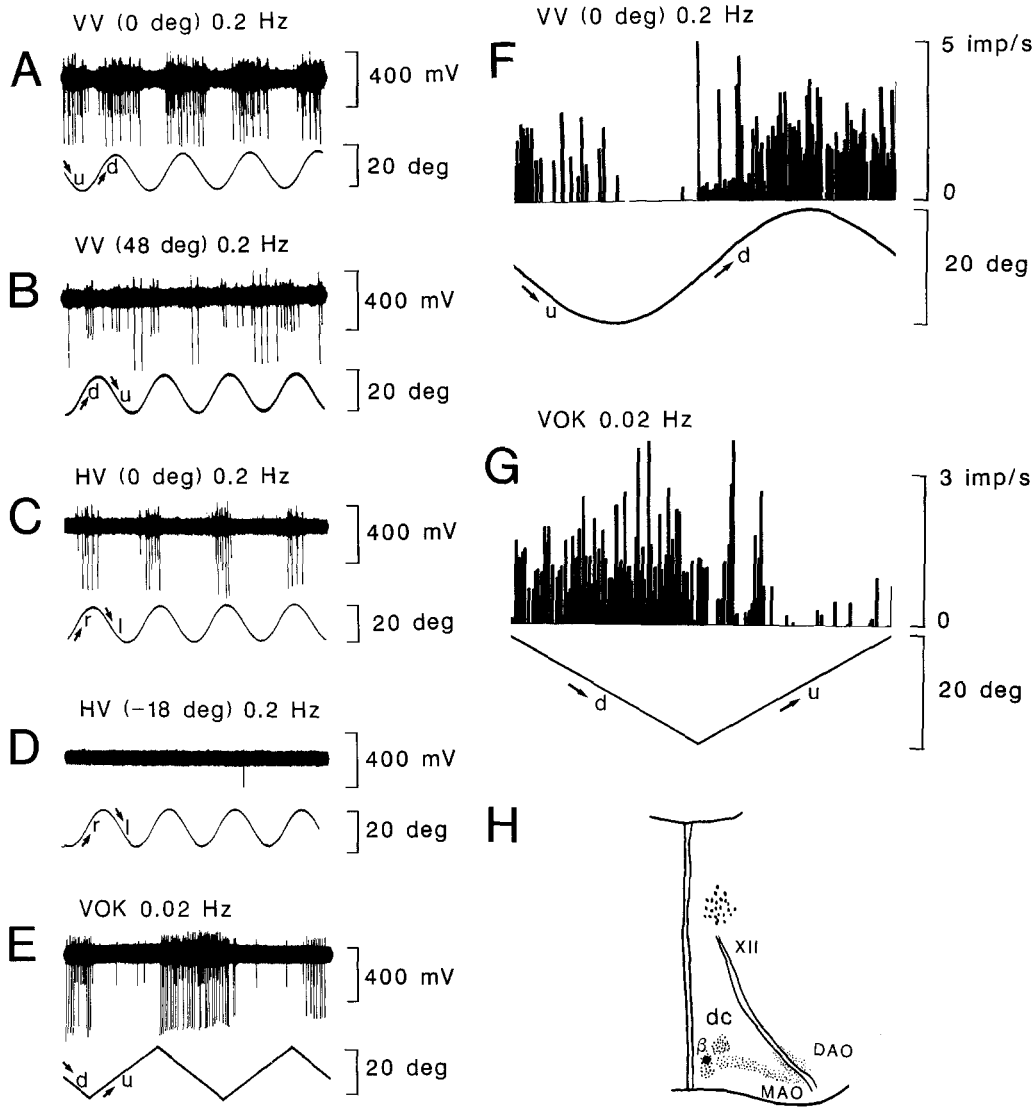
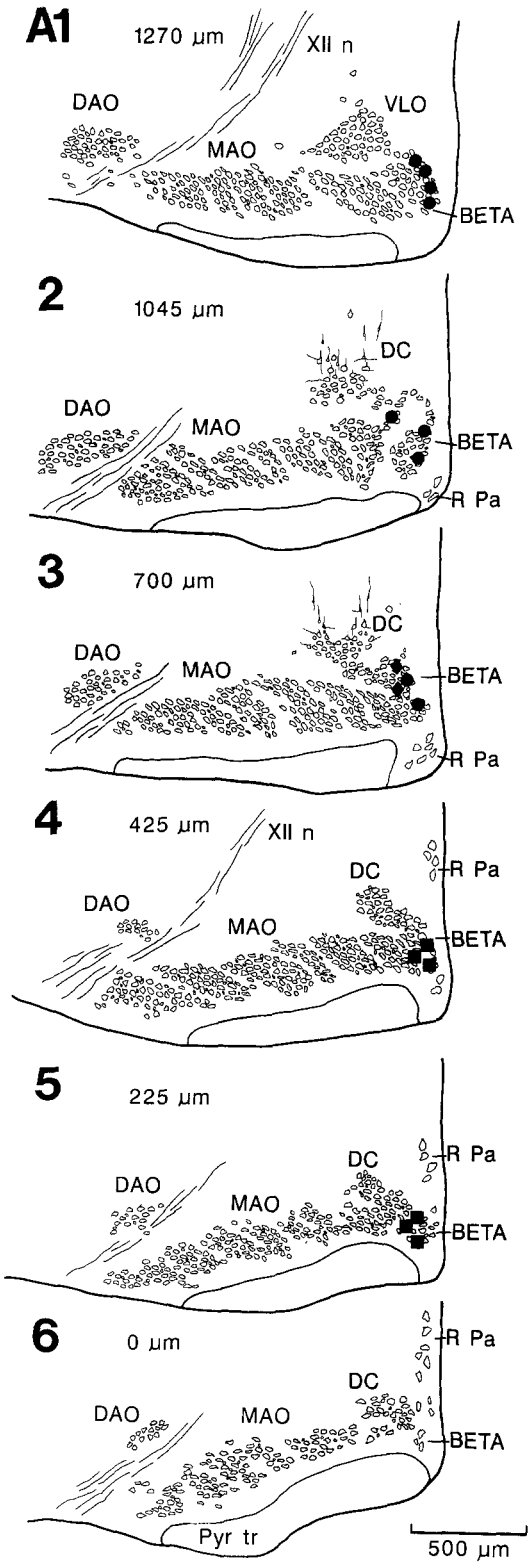


Fig. 6A–H. "Null point" measurement of vestibularly and optokinetically modulated neurons located in the rostral right β-nucleus. **A** Modulated activity was evoked by sinusoidal vestibular stimulation at 0.2 Hz in two neurons. The axis of stimulation was collinear with the longitudinal axis. Both the neuron with the larger action potential and the neuron with the smaller action potential discharged in phase with head position. The *arrows* in the *lower stimulus trace* refer to the position of the left side during roll stimulation. **B** When the axis of the head was shifted 48 deg in the clockwise direction (viewed from above) with respect to the rotation axis, the phase of the neuron with the larger action potential shifted with respect to the forcing function by 180 deg. The "null point" for this response – the head position at which no modulated activity was evoked – was 44 deg in the clockwise direction. This null point would correspond to the orientation of the right posterior and left anterior semicircular canal. The null point for the neuron with the smaller action potential was 53 deg. **C** Vestibular stimulation in the horizontal plane (yaw) evoked a modulated response in both neurons. **D** This response was eliminated when the head was tilted 18 deg to the right, bringing the right posterior semicircular canal into a null position. **E** Vertical optokinetic stimulation, using a triangular velocity waveform, of the left eye in the downward direction also evoked discharge from both β-nucleus neurons. The *arrows* in the *lower stimulus* trace refer to movement of the optokinetic stimulus with respect to the left eye. **F** Peristimulus histogram of the neuron with the larger action potential evoked by sinusoidal roll vestibular stimulation about the longitudinal axis. The bin width corresponds to 2 deg, and 80 stimulus cycles were averaged. The *arrows* refer to the position of the left side during roll stimulation. **G** Peristimulus histogram of the neuron with the larger action potential evoked by vertical optokinetic stimulation. The binwidth corresponds to 2 deg, and 20 stimulus cycles were averaged. The *arrows* in the *lower stimulus trace* refer to movement of the optokinetic stimulus with respect to the left eye. **H** The recorded neurons were located in the β-nucleus, just below the rostral dorsal cap, 100 μm caudal to the ventrolateral outgrowth. β, β-nucleus; *DAO*, dorsal accessory olive; *dc*, dorsal cap; *MAO*, medial accessory olive; *XII*, hypoglossal nerve

Distribution of null points for vestibularly driven neurons of the β-nucleus

The null points recorded from neurons in the β-nucleus clustered about two axes, corresponding to the orientation of pairs of vertical semicircular canals. The null points of neurons located in the caudal 500 μm of the β-nucleus were aligned with a plane passing through the planes of the ipsilateral anterior–contralateral posterior semicircular canals. These caudally located neurons had



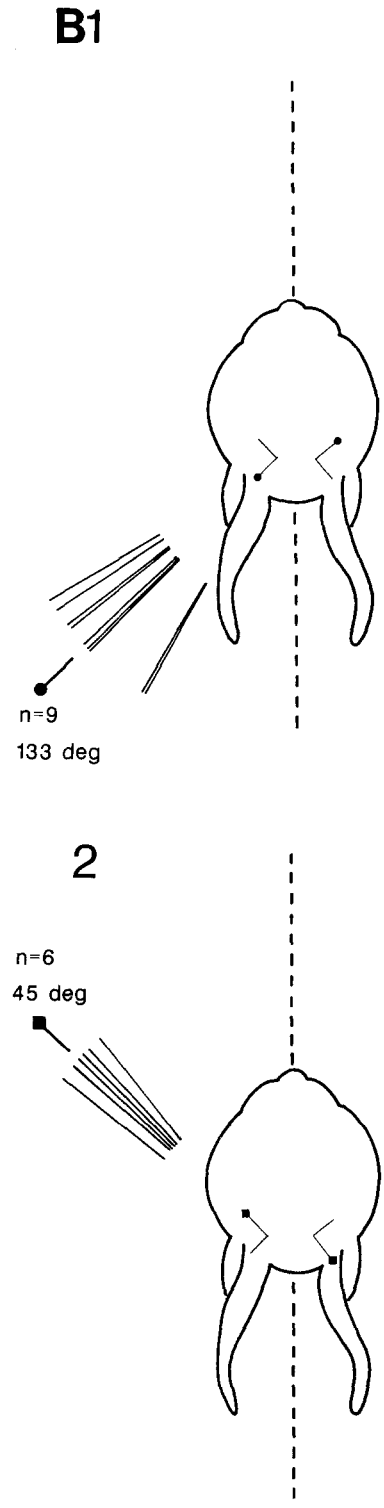


Fig. 7A,B. Distribution of neurons within the β-nucleus for which null point measurements were made. Sinusoidal vestibular stimulation about the longitudinal axis was used to evoke activity of neurons in the β-nucleus. By shifting the head in the clockwise or counter-clockwise direction, it was possible to determine a "null point" in 15 neurons. The These "null points" clustered around two planes that corresponded to optimal orientations of pairs of vertical semicircular canals (45 deg and 135 deg). The locations of β-nucleus neurons with measured null points are illustrated in **A**. These locations are represented as though all the recordings were made from the left β-nucleus. The *filled circles* indicate neurons with null points consistent with vestibular modulation originating from the left posterior–right anterior semicircular canals. The *filled squares* indicate the location of neurons with null points consistent with vestibular modulation originating from the left anterior–right posterior semicircular canals. The *filled diamonds* indicate the location of two neurons for which mull points could not be determined. **B1,2** The figurines illustrate the null points of each of these β-nucleus neurons. **B1** Null points consistent with vestibular modulation originating from neurons with left posterior–right anterior semicircular canal sensitivity (*filled circles*). These neurons had a mean optimal orientation of 133 deg and were clustered in the rostral β-nucleus. **B2** Null points consistent with vestibular modulation originating from neurons with left anterior–right posterior semicircular canal sensitivity (*filled squares*). These neurons had a mean optimal orientation of 45 deg and were clustered in the caudal β-nucleus

a mean null point of 45 deg with respect to the sagittal plane (Fig. 7A4–6, B2). Neurons located in the more rostral region of the β-nucleus were aligned with a plane passing through the planes of the ipsilateral, posterior–contralateral anterior semicircular canals. These more rostrally located neurons had a mean null point of 133 deg with respect to the sagittal plane.

Two neurons were recorded in which the null point could not be determined (filled diamonds, Fig. 7A3). The phase of the modulated vestibularly evoked activity could only be shifted by 180 deg when the head was rotated by more than 90 deg in either direction. These two neurons had no static vestibular sensitivity, suggesting that their activity could not be attributed merely to a summated otolithic signal.

Discussion

Technical limitations in recording from olivary neurons for prolonged periods

Physiological experiments aimed at deciphering the encoding properties of neurons in the IO are confronted by three major difficulties: (1) the IO is located in a region of the brainstem that is subject to movement artifacts created by respiration, heart beat and, during vestibular stimulation, gravitationally induced movement of the brain. (2) The action potential of many olivary neurons, unlike the action potentials illustrated in Figs. 2 and 3, can sometimes vary in amplitude. This variation, is unrelated to movement artifact, and has been observed by other investigators using intracellular recording techniques (Crill 1970; Benardo and Foster 1986). The variation in spike amplitude might be due to electrotonic coupling observed in olivary neurons (Llinas et al. 1974; Sotelo et al. 1974). (3) The low frequency of discharge of olivary neurons and low frequencies of stimulation to which neurons of the β-nucleus are responsive extends the time during which evoked activity must be monitored. For example, we routinely recorded 20 trials of sinusoidal vestibular stimulation at 0.02 Hz to test the vestibular sensitivity of β-nucleus neurons. This required a sampling period of at least 16 min. Because of these technical limitations, we could not explore fully the relationship between vestibular and optokinetic responses of individual olivary neurons. However, the four principal observations of this investigation are well supported. These observations are: (1) The activity of neurons of the β-nucleus was modulated by vestibular stimulation related to the vertical semicircular canal and otoliths. (2) Contrary to previous investigations, we could find no evidence for a functional input to the β-nucleus originating from the horizontal semicircular canals (Precht et al. 1976; Robinson et al. 1988). (3) Vestibularly modulated activity of β-nucleus neurons *decreased* when the rabbit was rolled onto the side that was ipsilateral to the recording site. (4) There is a topographic separation within the β-nucleus of vestibular inputs originating from the vertical semicircular canals.

Vestibularly evoked activity in neurons in the β-nucleus

The activity of β-nucleus neurons was modulated only by signals originating from the vertical semicircular canals and otoliths. This clearly contradicts earlier interpretations of the experimental observations that horizontal vestibular stimulation evoked climbing fiber activity recorded at the level of the cerebellar nodulus (Precht et al. 1976) or at the level of the β-nucleus (Robinson et al. 1988). In these instances, it is likely that the weakly vestibularly modulated activity evoked by vestibular stimulation about the vertical axis (yaw) was actually due to stimulation of the vertical semicircular canals. In both of these investigations, the experimental rate tables were not able to deliver rotation about the longitudinal axis. The present data are in good agreement with our recent recordings of vestibularly evoked CFRs in Purkinje cells of the cerebellar nodulus (Barmack and Shojaku 1989; Shojaku et al. 1991; Barmack and Shojaku 1992b). In these experiments, we were unable to record any CFRs that were driven best by rotation about the vertical axis (yaw). It is possible that there are other regions of the IO in which there is a representation of the horizontal semicircular canals, and that in the present experiment we did not sample the activity from these regions. However, if these regions do exist, they do not include the β-nucleus and they do not project to the nodulus.

Vestibularly evoked inhibition of activity in neurons in the β-nucleus

The activity of β-nucleus neurons was *decreased* when the rabbit was rolled onto the side ipsilateral to the recording site. The vestibular projection to the β-nucleus originates primarily from the ipsilateral DVN and part of the MVN (Walberg 1974; Saint- Cyr and Courville 1979; Barmack et al. 1993b). These observations are consistent with immunohistochemical evidence demonstrating that the β-nucleus of the rabbit receives a rich GAD-positive projection, and that this GABAergic input originates from the medial and descending vestibular nuclei (Nelson et al. 1986; Nelson et al. 1989). Obviously, additional intracellular and pharmacological experiments are necessary to demonstrate that this GABAergic pathway is the pathway by which vestibular information recorded in the present experiment is transmitted to the β-nucleus. We infer from our present results that this GABAergic projection is functionally inhibitory.

Our findings also raise the question as to whether a GABAergic inhibitory pathway is the only source of vestibular information to either the β-nucleus or other subdivisions of the IO. For example, the dorsal medial cell column receives a descending input from the vestibular complex (Saint-Cyr and Courville 1979). In preliminary recordings from this region, we have found neurons that are modulated by static vestibular stimulation of the otoliths. These neurons were also excited when the rabbit was rolled onto its contralateral side (Barmack and Fagerson, unpublished).

Topographic map of vertical vestibular information at the level of the inferior olive and in the climbing fiber projection onto the nodulus

In the present experiment, we have demonstrated a semicircular canal-specific projection onto the β-nucleus; namely, the ipsilateral anterior–contralateral posterior semicircular canals modulate the activity of neurons in the caudal 600 μm of the β-nucleus. A projection from the ipsilateral posterior and contralateral, anterior semicircular canal modulates the activity of β-nucleus neurons in a region that is 600–1200 μm rostral to the caudal pole of the β-nucleus. Previous neuroanatomical investigations have demonstrated a differential projection of the caudal and rostral regions of the β-nucleus onto the sur-

face of the uvula-nodulus. The caudal β-nucleus projects onto a midline region of the uvula-nodulus. The rostral region of the β-nucleus projects onto a more lateral zone of the uvula-nodulus (Sato and Barmack 1985; Kanda et al. 1989).

We have observed a mapping of CFRs recorded from a medial sagittal strip in the cerebellar uvula-nodulus. The CFRs of this medial strip are excited by rotation onto the ipsilateral side and have null points indicative of an ipsilateral posterior–contralateral anterior semicircular canal input (Barmack and Shojaku 1992b). Conversely, a more lateral sagittal strip is composed of Purkinje cells whose CFRs are excited by rotation onto the ipsilateral side which is indicative of an ipsilateral anterior and contralateral posterior semicircular canal input (Barmack and Shojaku 1992b). This functional mapping agrees both with the topographic maps based on retrograde tracer studies and with the functional measurements made in the present experiment.

In the present experiment, we recorded from two neurons that were excited by contralateral side-down rotation and that were localized to a region of the β-nucleus which appeared to be a transition zone between the representation of the semicircular canals. We could not determine canal-specific null points for these neurons. In fact, a phase shift of the modulated activity could only be produced by a head rotation of 90 deg for both of these neurons. Such null points might be characteristic of otolith responses. However, both of these neurons had no static vestibular sensitivity. The possibility exists that these cells received a vestibular innervation from both the ipsilateral anterior and posterior semicircular canals.

We have characterized the null points of β-nucleus neurons in terms of coplanar vertical semicircular canals, i.e., ipsilateral anterior–contralateral posterior semicircular canals. In fact, in the present experiment, we could not determine if the activity of β-nucleus neurons was modulated from both ipsilateral and contralateral semicircular canals. Additional experiments in rabbits with "plugged" semicircular canals would be required to answer this question.

The functional topographic map which we have described at the level of the β-nucleus and at the level of the cerebellar nodulus might encode a vestibular-visual space in a mediolateral gradient on the surface of the nodulus. This mediolateral gradient could provide a coordinate system for encoding all degrees of postural responses, from "backward" to "lateral" to "forward", evoked by stimulation of the vestibular-optokinetic system. Thus activation of CFRs in a medial strip of cerebellar Purkinje cells would signal an ipsilateral-backward fall, corresponding to activation of the ipsilateral posterior–contralateral anterior semicircular canals. Activation of CFRs in the lateral strip of Purkinje cells would signal an ipsilateral-forward fall, corresponding to activation of the ipsilateral anterior–contralateral posterior semicircular canals. Thus, this mediolateral gradient on the surface of the uvula-nodulus could bias the control of skeletal muscles involved in maintenance of balance, so that appropriate postural responses are evoked by vestibular stimulation. Some of the postural responses could change by as much as 180 deg, depending on whether an animal was falling forward or falling backward.

Functional interpretation of the vestibular pathway to the β-nucleus

A rough schematic diagram of the pathways involved in both visual and vestibular control of reflex pathways is illustrated in Fig. 8. More than 70% of primary vestibular afferents project directly to the ipsilateral cerebellar nodulus, where they terminate in the granule cell layer as mossy fiber terminals (Barmack et al. 1993a). Primary vestibular afferents also terminate in the vestibular complex. The transmitter for primary vestibular afferents has not been identified conclusively, but it is probably glutamate or aspartate (Dememes et al. 1984; Raymond et al. 1984). Secondary vestibular afferents originating from the caudal medial and descending vestibular nuclei project bilaterally to the nodulus of the cerebellum. The transmitter for this pathway is acetylcholine (Barmack et al. 1992). Secondary vestibular afferents originating from the medial and descending vestibular nuclei also project to the β-nucleus. This projection is GABAergic (Walberg 1974; Saint-Cyr and Courville 1979; Nelson et al. 1986; Nelson et al. 1989; Barmack et al. 1993b). Climbing fibers originating from the β-nucleus synapse in both the contralateral uvula and nodulus (Alley et al. 1975; Masumitsu and Sekitani 1991). The transmitter for this pathway is probably glutamate or aspartate (Wiklund et al. 1982; Matute et al. 1987), as well as the neuropeptide corticotropin releasing factor (Wynn et al. 1984; DeSouza et al. 1985; DeSouza 1987; Mugnaini and Nelson 1989; Barmack and Young 1990).

This circuitry might be expected to function as follows. An excitatory primary vestibular afferent signal originating from the right labyrinth would excite the right vestibular nuclei directly. The GABAergic pathway from the descending vestibular nucleus to the right β-nucleus would inhibit the spontaneous activity of the climbing fibers originating from the right β-nucleus and which synapse upon the Purkinje cells of the left uvula-nodulus. This reduction in climbing fiber input would cause increased SSs in Purkinje cells and a consequent increased Purkinje cell-induced inhibition of the left vestibular nuclei. Consequently, a primary afferent evoked discharge of secondary neurons in the vestibular nuclei on one side of the brainstem would cause, through this central circuitry, a reduction in secondary vestibular activity in the contralateral vestibular nuclei induced by Purkinje cell inhibition. (The Purkinje cell inhibitory pathway to the vestibular complex is not shown in Fig. 8).

Implicit in this argument is the assumption that the activity of Purkinje cells of the cerebellar nodulus is strongly influenced by vestibular driven climbing fiber inputs, perhaps by the frequently discussed climbing fiber-induced pause in SSs. This climbing fiber-induced pause is of variable duration, lasting from 15–30 ms (Granit and Phillips 1956) to several hundred milliseconds (Bell and Grimm 1969). It is dependent on anesthesia (Bloedel and Roberts 1971), as well as the specific

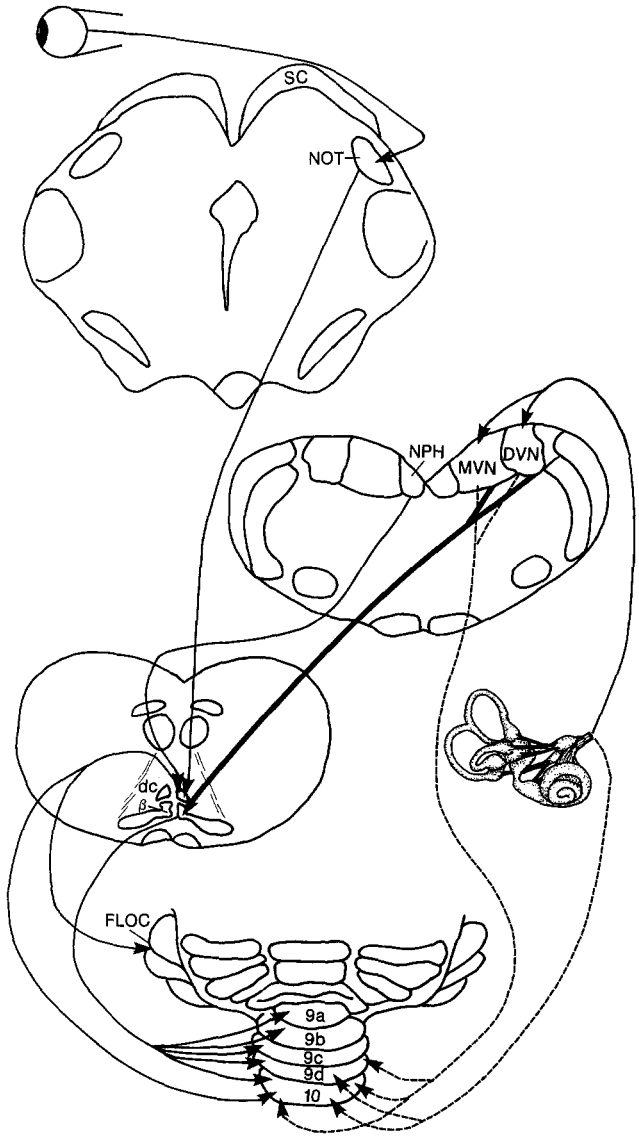


Fig. 8. Possible functional connections of the β-nucleus of the inferior olive. The β-nucleus climbing fiber projections terminate upon Purkinje cells in the contralateral uvula and nodulus. The GABAergic Purkinje cells of these structures project onto the subjacent vestibular nuclei (not illustrated). The vestibular primary afferent projections to the nodulus and to the vestibular nuclei are shown. The medial and descending vestibular nuclei project to the ipsilateral β-nucleus (*heavy lines*) and bilaterally to the nodulus and uvula (*dashed lines*). The dorsal cap receives a visual projection from the contralateral eye via the nucleus of the optic tract, and also receives a cholinergic input from the contralateral nucleus prepositus hypoglossi. The dorsal cap projects to the contralateral flocculus and ventral aspect of the nodulus. The vestibular secondary afferent cholinergic projection to the nodulus is also illustrated. β, β-nucleus; *dc*, dorsal cap; *DVN*, *MVN*, descending and medial vestibular nuclei; *FLOC*, flocculus; *NOT*, nucleus of the optic tract; *NPH*, nucleus prepositus hypoglossi; *SC*, superior colliculus; *9a–d*, uvula; *10*, nodulus

method of stimulating climbing fibers. In this regard, the relationship between "spontaneous" (i.e., experimentally uncontrolled) CFRs and SSs appears to be variable (Bell and Grimm 1969; McDevitt et al. 1982; Sato et al. 1992). This variability may reflect a lack of control of the climbing fiber input, as well as a lack of control of the accurate knowledge with regard to the spatial organization of the cerebellar cortex with respect to the particular climbing fiber afferent system being studied. In recordings from Purkinje cells in the nodulus, we have observed a pause in SSs following vestibularly-evoked CFRs and this pause was inversely proportional to the initial discharge frequency of SSs (Barmack and Shojaku 1992b).

The vestibulo-olivo-cerebellar climbing fiber pathway could provide a more centrally regulated signal capable of overriding signals conveyed to the nodulus via mossy fiber pathways from both primary and secondary vestibular afferents. Alternatively, the interactions between climbing fiber signals and afferent signals conveyed by mossy fibers may provide some of the basis for the participation in this circuitry in optokinetic and vestibular reflex adaptation (Barmack and Shojaku 1992a).

Acknowledgements. We thank Leta Guptill for expert histological, technical and artistic assistance. This research was supported by NEI EY04778, the Oregon Lions Sight and Hearing Foundation, and NICDS NS09904.

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