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LESIONS IN THE CAT PREPOSITUS COMPLEX: EFFECTS ON THE VESTIBULO-OCULAR REFLEX AND SACCADES

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SUMMARY

1. The effects of bilateral electrolytic lesions within and around the prepositus hypoglossi (p.h.) nucleus on horizontal saccades in the dark and on the horizontal sinusoidal vestibulo-ocular reflex (v.o.r.) in the dark were studied.

2. After p.h. lesion, including its rostral part between P 7 and P 8, the v.o.r. showed a phase lead as much as about 90 deg at 0·10 Hz. A significant gain reduction paralleled that phase lead at lower frequencies. A large post-saccadic drift was also observed, the time constant of which ranged from 0·3 to 0·6 s.

3. After p.h. lesion extending from P 8 to P 11 (but sparing the rostral part of the p.h.), no significant gain or phase lead change was observed. Post-saccadic drift was either missing or weak.

4. A bilateral medial vestibular nucleus (m.v.n.) lesion from P 7 to P 11 produced a marked gain decrease, paralleled by a marked phase advance. A post-saccadic drift was observed ($\tau = 0{\cdot}6$ s).

5. A surgical mid-line lesion from P 7 to P 11 (depth: about 2 mm) was followed by no remarkable change in the gain and in the phase of the v.o.r. No post-saccadic drift was observed after such lesion.

6. It was concluded that (i) both the horizontal v.o.r. integration processing, and the horizontal saccadic integration processing were destroyed when an electrolytic lesion was made 'in the region of' the rostral part of the p.h. nucleus, and that (ii) the posterior four-fifths of the p.h. was the location of neither the horizontal v.o.r. integrator nor the horizontal saccadic integrator.

INTRODUCTION

More than 10 years ago, it was proposed that a neural integrator (in the mathematical sense of the word) must be a major signal-processing element in the central pathways subserving the vestibulo-ocular reflex (Skavenski & Robinson, 1973) and the saccades (Young & Stark, 1963). This concept is now generally accepted (see Robinson, 1981). However, the location of this (or these) integrator(s) is still debated. The present paper is concerned with this important question.

In the dark, any rotation of the head generates automatically a compensatory eye movement (vestibulo-ocular reflex or v.o.r.). In 1973, Skavenski & Robinson drew

the attention to the fact that, when the v.o.r. is working during sinusoidal head rotations over the range of about 0·01–1·5 Hz, changes of eye position in the head are just equal and opposite to changes of head position in space. Since the semicircular canals, which sense head rotation, are stimulated by angular acceleration of the head, Skavenski & Robinson (1973) concluded that head acceleration must be integrated twice to produce eye position. Over the range of about 0·05–1 Hz, the firing rate of the primary semicircular afferents is proportional not to head acceleration but to head velocity (Fernandez & Goldberg, 1971; Blanks, Estes & Markham, 1975). Therefore the first integration is accomplished mechanically in the semicircular canals (Steinhausen, 1933). The velocity signal must be integrated again by a neuronal network in order to yield the eye command signal (Skavenski & Robinson, 1973). This network is the 'v.o.r. integrator'.

In both the dark and light the gaze can jump from one point to another by rapid rotations of the eyeball, the saccades, separated by fixation periods. The oculomotoneurone signal generating this type of movement is a pulse-step signal (Robinson, 1964). The pulse, that is a short burst of high-frequency motoneurone firing, serves to move the eye during the saccadic movement; the step, that is a regular motoneurone firing of lower frequency, serves to hold the eye in its new position. There are in the paramedian reticular formation 'burst neurones' which discharge only before and during the saccadic movement but not during the subsequent gaze holding (Keller, 1974); this type of short discharge can be approximated to a pulse signal. From this experimental fact, it was hypothesized that the step signal could be obtained by the processing of the pulse in an integrator (the saccadic integrator); the pulse and the step signals could then be combined.

It is generally believed that the v.o.r. and the saccadic system share a final common integrator (Robinson, 1975, 1981) although some doubt subsists (see Godaux & Laune, 1983). Nevertheless, several nuclei are candidates for the integrator(s) underlying structure(s). The integrator is known to be dependent on, but not localized in the cerebellum. After cerebellectomy, a post-saccadic drift (Westheimer & Blair, 1974; Robinson, 1974; Godaux & Vanderkelen, 1984) and a phase advance of the v.o.r. are observed (Keller & Precht, 1979; Godaux & Vanderkelen, 1984), but these modifications are clearly smaller than those expected in the case of a total integrator loss. At present the more likely candidates are: the pontine paramedian reticular formation (Cohen & Komatsuzaki, 1972), the medial vestibular nucleus (m.v.n.; Robinson, 1975) and the prepositus hypoglossi (p.h.) nucleus (Lopez-Barneo, Darlot, Berthoz & Baker, 1982). 'Tonic units' which discharge as a function of eye position and not of eye velocity are found in each of these three nuclei (Keller, 1974; Keller & Daniels, 1975; Fuchs & Kimm, 1975; Lopez-Barneo *et al.* 1982). More recently, Galiana & Outerbridge (1984) proposed a model in which the vestibular internuclear commissural pathway plays a major role in the integration processing.

In this paper we studied the behaviour of the integration processing (through the post-saccadic drift in the dark and the frequency analysis of the v.o.r. in the dark) after making different lesions of the p.h. nucleus, of the m.v.n. and of some vestibular commissural fibres.

METHODS

General procedure

Eleven alert cats (2·3–3·2 kg) were used in this study. Under general anaesthesia (xylidino-dihydrothiazin, Rompun, Bayer, 3 mg/kg, and pentobarbitone, Nembutal, Abbott, 20 mg/kg) aseptic surgery was performed and the animals implanted with two chronic devices: a dental cement platform bolted to the skull for immobilizing the head and a pair of silver/silver chloride electrodes for horizontal electro-oculography (e.o.g.) recording. 8 days after surgery each animal was trained to accept restraining conditions without stress. Control recordings were then carried out, with the alertness of the cat being maintained by intramuscular injection of amphetamine (0·5 mg/kg) 15 min before each experimental session. Calibration of the traces was obtained by rotating the cat sinusoidally ($\pm$20 deg) surrounded by a fixed lighted drum (Keller & Precht, 1979). The mean of the peak-to-peak amplitudes of the compensatory slow-phase eye movement recorded at the different tested frequencies (0·05, 0·10, 0·15, 0·25, 0·5 and 1 Hz) was assumed to be equal to the peak-to-peak amplitude of the forced head movement during these conditions of vestibular stimulation (Keller & Precht, 1979). Under the same conditions of dark adaptation, the fluctuations of this value from one day to another were less than 5%. As the e.o.g. varies with dark–light adaptation, some problems emerge when a calibration in the light is used for eye movements recorded in the dark. Therefore, in order to reduce dark adaptation and the resulting e.o.g. changes, the requisite periods of darkness were as short as possible and separated from each other by a 1 min illumination period. Under these conditions dark–light adaptation produced less than 5% fluctuation of the e.o.g. (Godaux, Gobert & Halleux, 1983, Fig. 1). E.o.g. was calibrated at the beginning of the experiment and every 15 min thereafter. Experiments never lasted for more than 1 h. Such measurements were taken repeatedly for each animal before the lesion and used as calibration for post-lesion measurements. The movement of the rotating frame was monitored by a potentiometer. Rotating frame and e.o.g. signals were amplified by an AM 502 Tektronix amplifier with a band-pass d.c. to 100 Hz. They were subsequently recorded on a pen-writer (Hewlett Packard, Model 7402 A) and stored on a magnetic tape (Philips, Ana-Log 7). After collecting the control recordings, the brain-stem lesion was performed. The animals were in good condition after this surgery. Eye movements were tested post-operatively on the 4th and the 7th days. The animals were killed on the 8th day.

Lesions procedures

The surgical procedure was performed aseptically under general anaesthesia using an operating microscope. In each of our eleven cats the posterior vermis was removed by gentle suction and the floor of the fourth ventricle exposed. The procedure was stopped at this step in two cats (cats 14 and 24), for controls. The surgical session was then continued by electrolytic lesions in seven cats and by scalpel lesions in two cats. For electrolytic destruction, electrodes made of 200 μm stainless-steel wires were introduced under visual control in the medulla using stereotactic techniques. Lesions were made by passing monopolar current (electrode negative) of 3 mA between the electrode tip and a reference surface electrode for 30 s.

In six cats (cats 16, 19, 21, 18, 25 and 26), the target structure was the p.h. nucleus, bilaterally. Three electrolytic lesions were made 1·2 mm lateral to each side of the mid line. In the rostrocaudal direction, the target coordinates were 8, 9 and 10 mm posterior to the external auditory meatus respectively. For each lesion, the tip of the electrode was placed at a depth of 0·5 mm from the surface of the medulla.

In one cat (cat 23) the target structures were the m.v.n., bilaterally. Three electrolytic lesions were made on each side of the brain (target stereotactic coordinates: L 2·4 and P 8, L 2·4 and P 9, L 2·4 and P 10).

In two other cats (cats 27 and 28), we attempted to destroy the decussating fibres at the level of the above lesions, that is from P 7 to P 11. The brain stem was cut in the mid line to a depth of 2–3 mm with a thin scalpel blade.

Stimulating device

The head of the cat was put in the centre of a turntable and placed so that the horizontal semicircular canals were nearly horizontal (10 deg up). The turntable could only move sinusoidally.

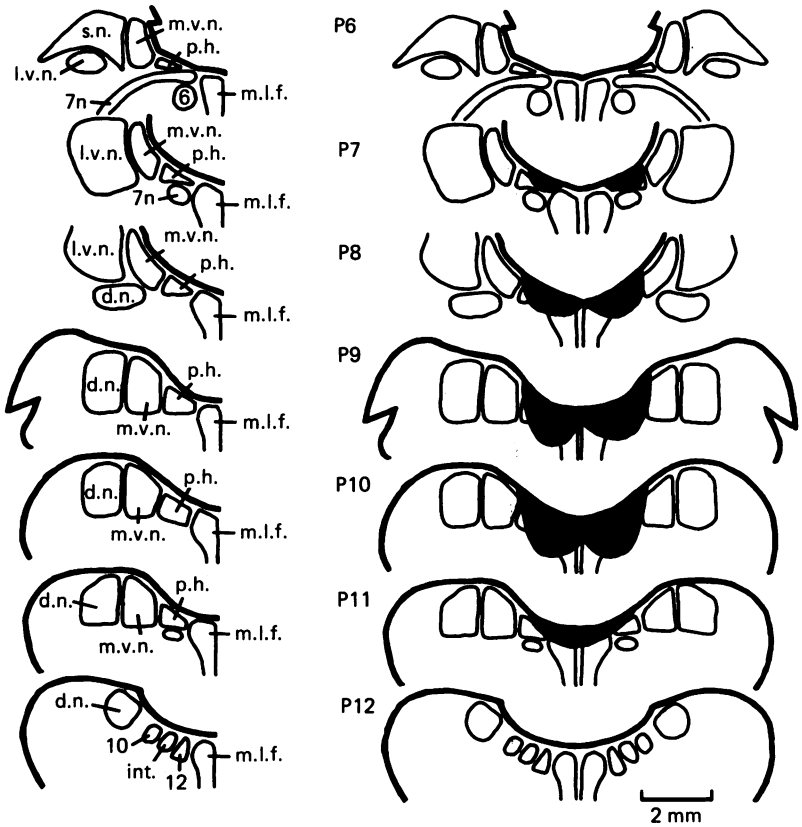

Fig. 1. Drawings of the extent of the bilateral prepositus lesion in cat 16. Histological reconstruction of the p.h. lesion. The level of each vertical stereotactic plane is indicated as P 6 to P 12. In order to avoid blurring, each histological section is shown twice: on the left is the reference drawing with appropriate labelling; on the right are black areas indicating the lesioned structures. s.n., superior nucleus; m.v.n., medial vestibular nucleus; l.v.n., lateral vestibular nucleus; p.h., prepositus hypoglossi nucleus; 6, abducens nucleus; 7n, nerve seven; m.l.f., medial longitudinal fasciculus; d.n., descending nucleus; 10, nucleus of nerve ten; 12, nucleus of nerve twelve; int., nucleus intercalatus. Notice that in order to reach the roof of the fourth ventricle, a posterior vermectomy was also performed in this cat.

Eye-movement tests

Only horizontal eye movements were considered in this paper. Two types of movement were investigated: (1) the saccades in the dark and (2) the sinusoidal v.o.r. in the dark. The only amplitude tested was ± 20 deg. Frequencies ranged from 0·05 to 1 Hz.

Data processing

For the v.o.r., the slow cumulative eye-position curves were constructed manually from the raw records (Meiry, 1966). Gain was defined as the ratio: peak-to-peak eye position/peak-to-peak rotating head position. Phase shift was designated as zero when eye and head movements were exactly opposite. Five to ten cycles were used. Furthermore, post-saccadic parts of the v.o.r. curves were not taken into account in building the slow cumulative eye position (see Fig. 1 in Godaux & Vanderkelen, 1984).

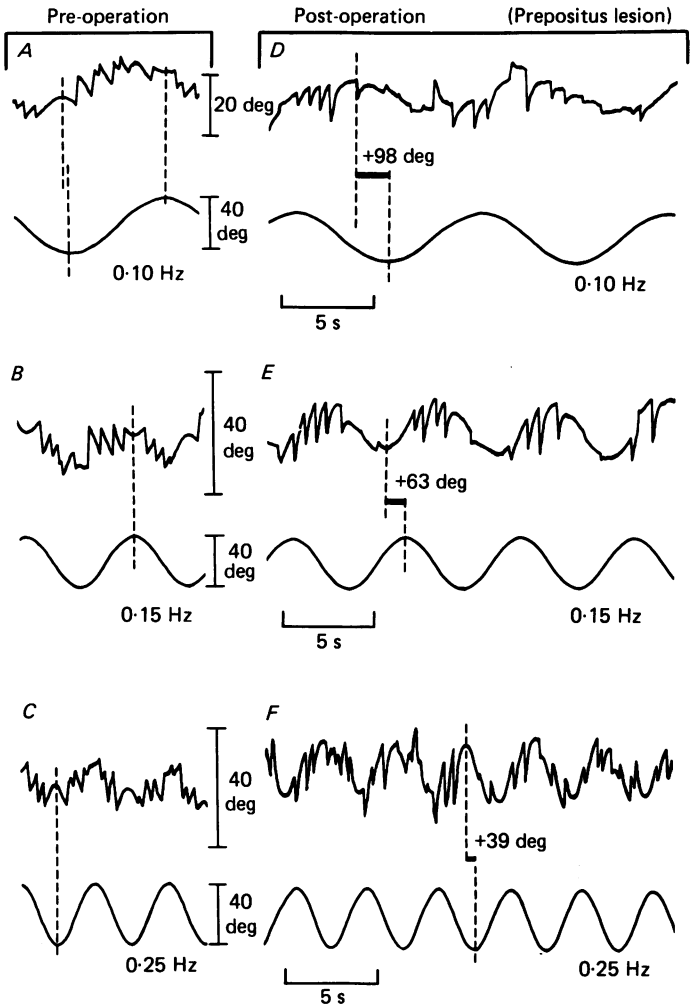

Fig. 2. Vestibulo-ocular reflex to sinusoidal head movements in one cat (cat 16) before (*A–C*) and after (*D–F*) bilateral p.h. lesion. In each block are displayed the eye movement (e.o.g. signal) (upper trace) and the head or turntable movement (lower trace). The amplitude of the sinusoidal stimuli is 20 deg throughout (one direction amplitude). The frequency of the turntable movement is 0·10 Hz in *A* and *D*, 0·15 Hz in *B* and *E*, and 0·25 Hz in *C* and *F*. The time calibration is the same throughout: 5 s. The vertical dashed lines point out the phase leads.

Histological controls

At the conclusion of an experiment, the cat was killed with an overdose of sodium pentobarbitone. The animal was perfused through the aorta with a 10% formalin solution. The brain stem was embedded in paraffin. Serial sections, 20 μm thick, were made. Every tenth section was mounted and stained with Cresyl Fast Violet for cell bodies. Another set of every tenth section was stained with Luxol Fast Blue for myelin. The location and extent of the electrolytic lesions were examined and plotted onto a schematic representation of the region on the scope. The atlas of Berman (1968) was used to help to interpret the histological sections.

RESULTS

The 'perihypoglossal complex' is situated in close proximity to the nucleus of the hypoglossal nucleus. It consists of three main nuclei: (1) the nucleus prepositus hypoglossi, (2) the nucleus intercalatus of Staderini and (3) the nucleus of Roller. In the cat, the caudal end of the prepositus hypoglossi (p.h.; Fig. 1), which fuses with the nucleus intercalatus (int.; Fig. 1), is situated dorsal to the rostral pole of the hypoglossal nucleus, 12. At its rostral end, the nucleus prepositus hypoglossi caps the genu of the facial nerve, 7 G.

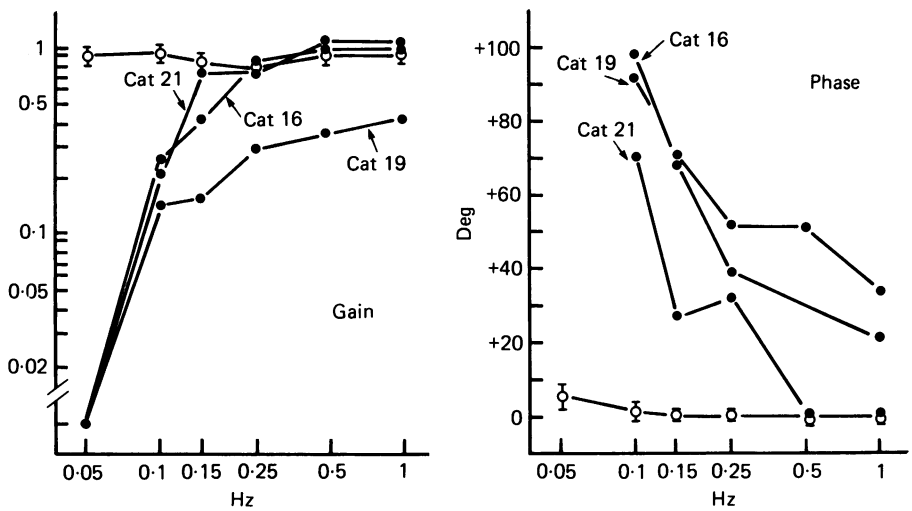

Fig. 3. Diagram of the gain and phase of the v.o.r. tested in the dark as a function of frequency (Bode plot) before (○) and after (●) bilateral prepositus lesion in three cats (cats 21, 19 and 16). For each frequency, the three individual values of the v.o.r. before the operation are averaged (○). The vertical bars on each side of the circle indicate the standard deviation ($n = 3$).

The part of the p.h. nucleus we will call here 'the rostral part of the p.h. nucleus' is situated between P 7 mm and P 8 mm, just behind the abducens nucleus.

Prepositus lesion including its rostral part

Placement of the lesions. Three cats (cats 16, 19 and 21) received electrolytic lesions in the p.h. nucleus. The extent of these lesions is shown in Fig. 1 for cat 16 (see also Pl. 1*A*). In the frontal plane, all the lesions were centred on the p.h. nucleus, bilaterally. The adjacent medial longitudinal fasciculus (m.l.f.) is nearly always lesioned in its superficial part. The lesions did not extend significantly in the m.v.n. region, except in the caudal part of the right lesion in cat 21. The rostral limit of the lesion was at P 6·4 mm for the left p.h. and at P 6·9 mm for the right p.h. in cat 16, at P 7·1 bilaterally in cat 19 and at P 7·5 mm for the left p.h. and at P 8 for the right p.h. in cat 21. The lesion ended between P 11 and P 12 for these three cats.

V.o.r. Gain and phase of the v.o.r. in the dark were seriously affected in the three cats (cats 16, 19 and 21). The most striking feature is the increase of the phase lead,

especially at lower frequencies. The pre- and post-operative phase leads are illustrated for cat 16 in Fig. 2. Fig. 3 shows the Bode plot of the v.o.r. for the three cats. At 0·10 Hz, the observed phase lead was +92 deg in cat 16, +98 deg in cat 19 and +74 deg in cat 21.

Saccades. The normal cat could easily hold a steady eye position after a saccadic movement in the dark (time constant above 20 s). The p.h. lesioned cats could not:

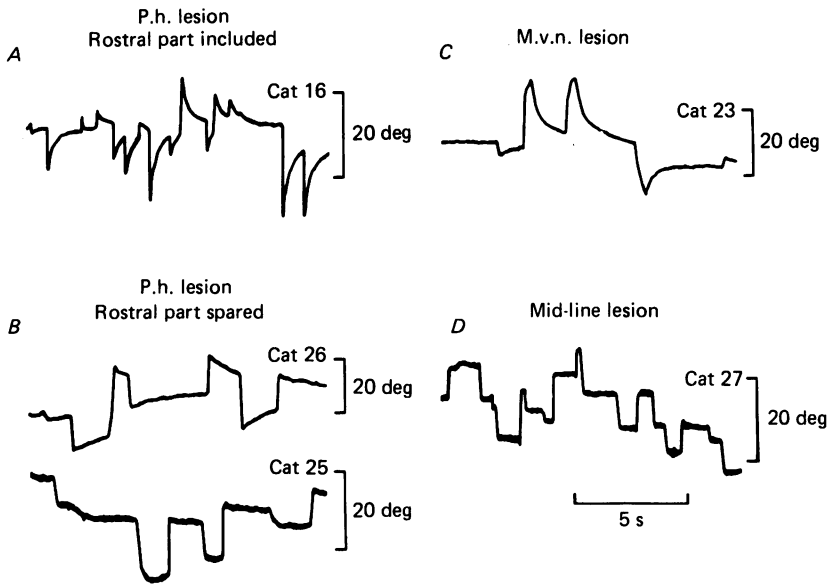

Fig. 4. Horizontal saccades recorded in complete darkness after different lesions. The saccades are spontaneous or acoustically induced. *A*, saccades after bilateral p.h. lesion including its rostral part (cat 16). *B*, saccades after bilateral p.h. lesion sparing its rostral part (cats 25 and 26). *C*, saccades after bilateral m.v.n. lesion (cat 23). *D*, saccades after mid-line lesion (cat 27). Notice the lack of failure of the gaze-holding system in cats 25 and 27.

after a saccade the eye position shifted towards a more central position. This post-saccadic slip was the major abnormality created by the lesion (Fig. 4*A*). This drift had an exponential profile. The measured time constant was 0·34±0·1 s ($n = 15$) in cat 16, 0·4±0·1 s ($n = 15$) in cat 19 and 0·8±0·2 s ($n = 15$) in cat 21. Prepositus lesion produced no striking change in saccadic velocity (Fig. 4*A*).

Prepositus lesion sparing its rostral part

Placement of the lesions. The lesions in three cats (cats 18, 25 and 26) are shown in Fig. 5*C*. The rostral limit of the lesion was at or behind P 8 mm in each cat (P 8 mm in cat 26; P 8·2 mm in cat 18 and P 10 mm in cat 25). The lesion ended between P 11 and P 12 in cats 18 and 26 and at P 13·5 mm in cat 25.

V.o.r. This was mildly affected in the three cats. In view of the extent of the lesion of the p.h. in these cats (Fig. 5*C*), this negative result must be pointed out (Fig. 5*A* and *B*). Only a very small increase in phase lead was observed. At 0·10 Hz the phase

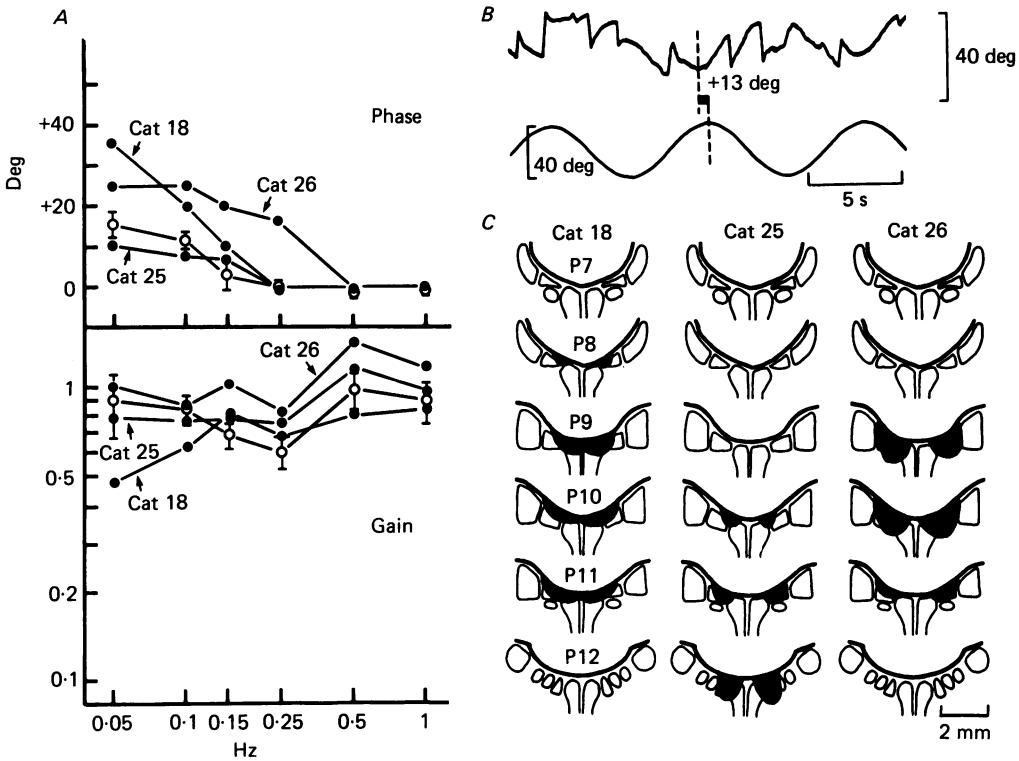

Fig. 5. *A*, Bode plot of the v.o.r. before (○) and after (●) bilateral p.h. lesion in three cats (cats 18, 25 and 26). For each frequency, the three individual values of the v.o.r. before the operation are averaged (○). The vertical bars on each side of the circle indicate the standard deviation ($n = 3$). *B*, v.o.r. in the dark in cat 26 before (*B*) and after (*C*) p.h. lesion. The upper trace is the eye movement (e.o.g. signal). The lower trace is the head movement (±20 deg, 0·10 Hz). *C*, drawing of the extent of the electrolytic lesions in cats 18, 25 and 26. The level of each vertical stereotactic plane is indicated (from P 6 to P 12). To identify the different structures see Fig. 1. Black areas mark the lesioned structures. Notice that in order to reach the roof of fourth ventricle a posterior vermectomy was also performed in each of the cats.

leads were +11, +12 and +13 deg before, +20, +8 and +25 deg after the lesion in cats 18, 25 and 26 respectively. There was no consistent change in the gains, post-operatively.

Saccades. A mild post-saccadic drift was observed in cats 18 and 26 (Fig. 4*B*). The time constant of the slip was 1·8±0·6 s ($n = 15$) in cat 18 and 2·0±0·3 s in cat 26 ($n = 15$). There was no post-saccadic drift at all in cat 25 (Fig. 4*B*).

M.v.n. lesion

Placement of the lesion. In cat 23 (Fig. 6*B*, Pl. 1*B*), the electrolytic lesion was centred on the m.v.n. bilaterally. The lesion extended from P 7 to P 11·5. It did not extend beyond the boundaries of m.v.n., except in P 9 where a small part of the p.h. was also lesioned.

V.o.r. The most striking feature of the v.o.r. of cat 23 tested in the dark was its

gain decrease (Fig. 6*A*). Except at frequencies of 0·5 and 1 Hz, there were only a few rapid resetting phases (Fig. 6*D*). Furthermore, the gain increased as a function of frequency. An increased phase lead of +64 deg at 0·10 Hz paralleled that low gain.

Saccades. The saccades showed a marked post-saccadic drift. The time constant of the exponential course of this latter was 0·6±0·1 s ($n = 15$) (Fig. 4*C*).

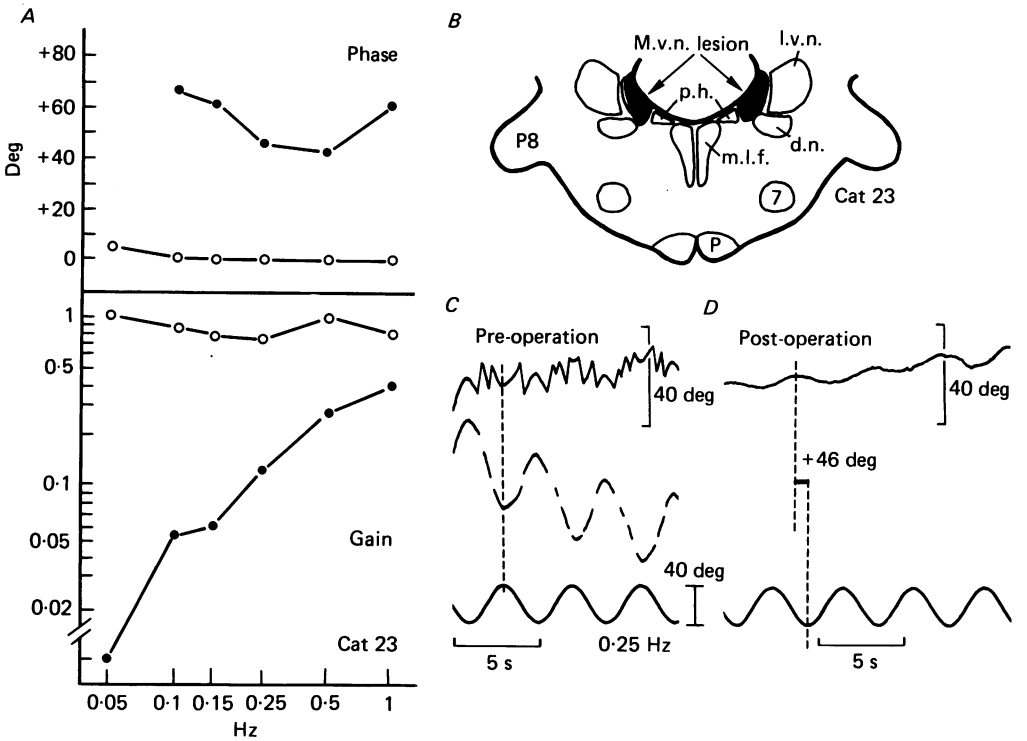

Fig. 6. *A*, diagram of the gain and phase of the v.o.r. tested in the dark before (○) and after (●) a bilateral m.v.n. lesion in cat 23. *B*, drawing of the lesion at the level P 8. For complete extent of the lesion, see the text. Abbreviations as in Fig. 1. *C*, v.o.r. tested in the dark before the operation at 0·25 Hz and with amplitude ±20 deg. The upper trace is the eye position signal (e.o.g. signal); the middle trace is the cumulative eye position curve and the lower trace is the head position curve. *D*, v.o.r. tested under the same conditions as in *C*, but after the m.v.n. lesion. The upper trace is the eye position signal; the lower trace is the head position curve.

Mid-line lesions

Placement of the lesions. A mid-line lesion was produced surgically in two cats (cats 27 and 28). In both cats the cut was in a parasagittal plane in the right m.l.f. (Fig. 7*B*, Pl. 1*C*) and extended from P 7 to P 11·6 in cat 27 and from P 7·5 to P 12·1 in cat 28. The maximal depth of the section was 1·4, 2·1 and 2 mm at P 7, P 8 and P 9 respectively in cat 27, whereas it was 1·4, 1·8 and 3·4 mm at P 7·5, P 8 and P 9 in cat 28.

V.o.r. This was only mildly affected by the present mid-line lesions: only small changes in gain and phase appeared after the operation. Fig. 7*A* and *C* depicts the

effect of mid-line lesions on the v.o.r. tested in the dark for cats 27 and 28. The phase lead increased slightly in cat 27 (from 6 to 23 deg at 0·10 Hz) but decreased slightly in cat 28 (from 22 to 0 deg at 0·10 Hz). No consistent and coherent change was observed in the pre- and post-operative gains.

Saccades. As illustrated in Fig. 4*D*, no saccadic drift was observed.

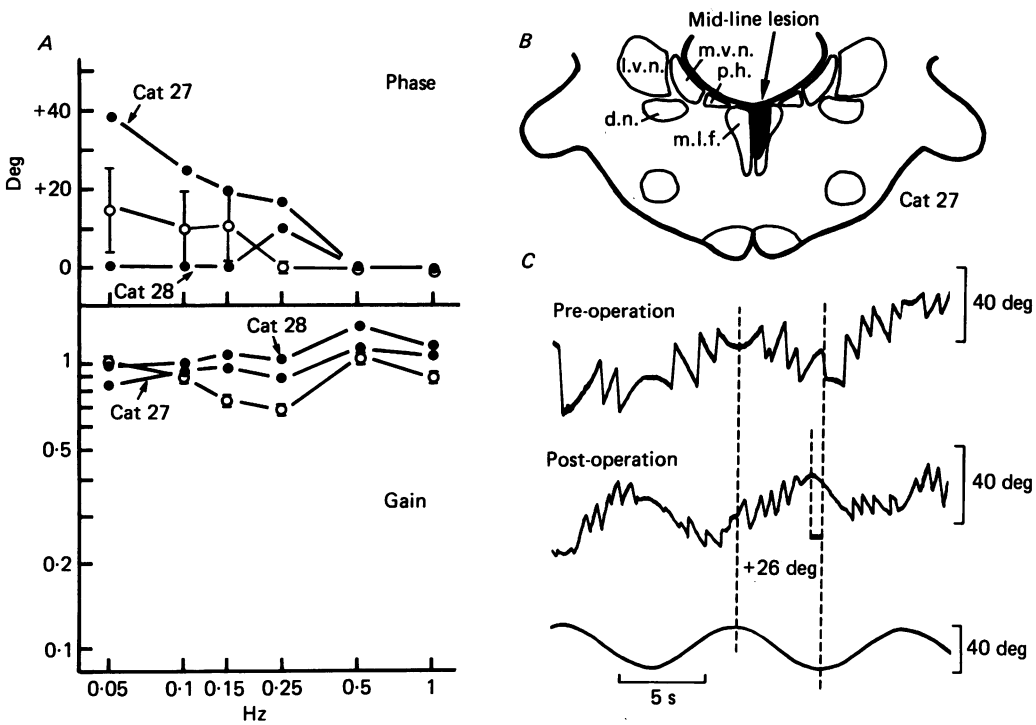

Fig. 7. *A*, diagram of the gain and phase of the v.o.r. tested in the dark before (○) and after (●) a mid-line lesion in the medulla in two cats (cats 27 and 28). For each frequency the two individual values of the v.o.r. before the operation are averaged (○). The vertical bars on each side of the circle indicate the standard deviation ($n = 2$). *B*, drawing of the lesion at the level P 8; abbreviations as in Fig. 1. *C*, v.o.r. tested in the dark (0·10 Hz, 20 deg) one direction amplitude before and after the mid-line lesion in cat 27. The upper trace is the eye position signal before the lesion. The middle trace is the eye position signal after the lesion. The lower trace is the head position signal. The vertical dashed lines point out the phase lead before (0 deg) and after (+26 deg) the mid-line lesion in cat 27.

Ablation of posterior vermis

In two cats, the lesion was confined to a posterior vermectomy, for comparison. The nodulus, uvula, pyramis, tuber and parts of the paramedian lobules were removed. Some parts of medial cerebellar nuclei were damaged. In one cat (cat 24), a spontaneous nystagmus beating to the right was present. Nevertheless, this nystagmus vanished after about 1 min in darkness. No post-saccadic drift in the dark was observed in these cats (Fig. 4*D*). The v.o.r. tested in the dark showed no consistent modification of the gain and of the phase at the tested frequencies.

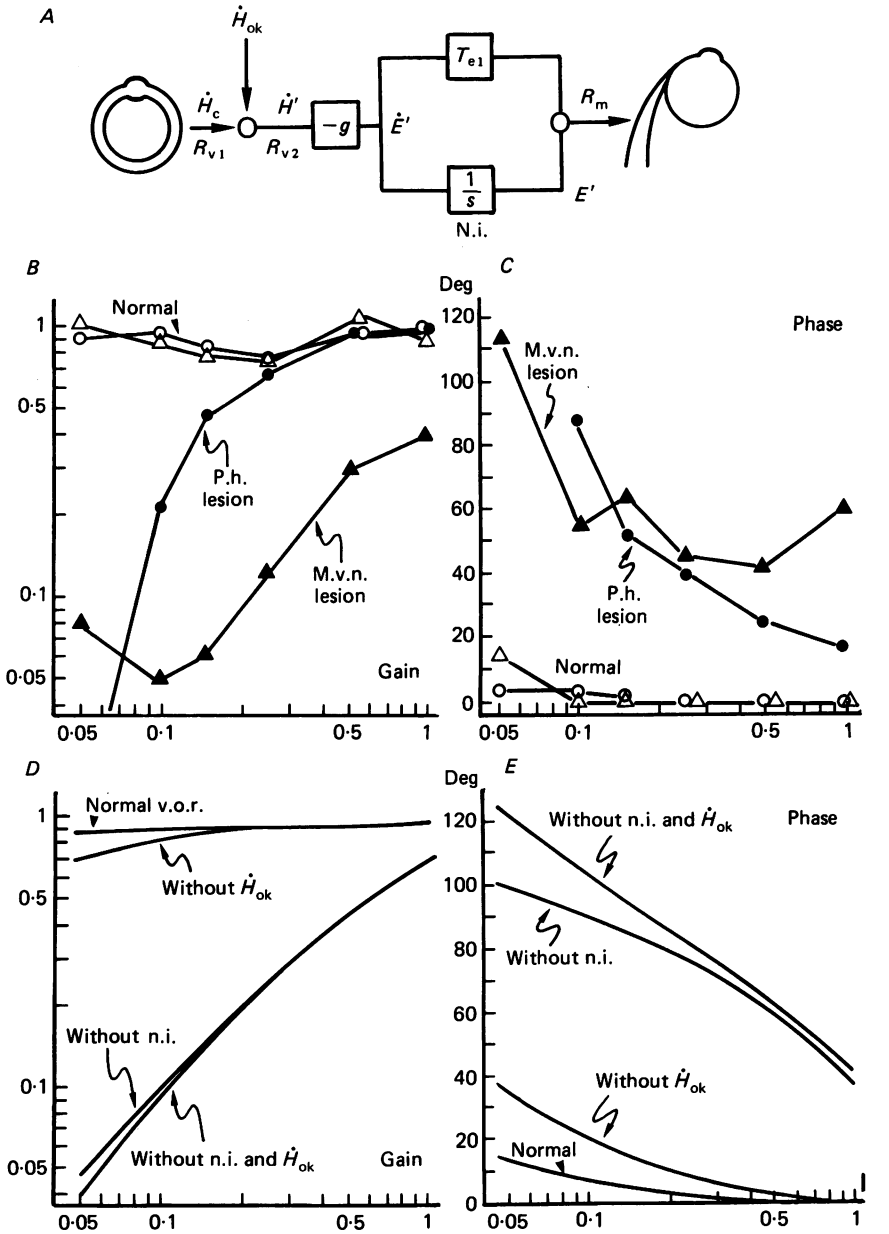

Fig. 8. *A*, Robinson's model (Robinson, 1977, 1981) of the v.o.r. tested in the dark. $\dot{H}_c$, head velocity as coded by the semicircular canals; $\dot{H}_{ok}$, a central signal that increases the time constant of the signal coming from the canals; R_{v1}, discharge rate of primary vestibular neurones; R_{v2}, discharge rate of second-order vestibular neurones; n.i., neural integrator; R_m, discharge rate of oculomotoneurones; $-g$, over-all reflex gain; T_{e1} is a time constant linked to the gain of the direct pathway (see Appendix). *B* and *C*, diagram of the gain and phase of the v.o.r. tested in the dark as a function of frequency before (○) and after p.h. lesion including its rostral part (●), before (△) and after m.v.n. lesion (▲). For each frequency the three individual values of the v.o.r. before and after p.h. lesion are averaged. *D* and *E*, computed gain and phase of the cat's v.o.r. tested in the dark following the model shown in *A* (see Appendix). Four curves were computed: the first with the intact model; the second when the $\dot{H}_{ok}$ signal is missing; the third when the n.i. is destroyed and the fourth when both the $\dot{H}_{ok}$ signal and the n.i. processing are missing.

DISCUSSION

Is the integration processing of the v.o.r. disturbed by our lesion?

We would like to discuss the modification of the v.o.r. in the dark by referring to the model of Robinson (Robinson, 1981) reproduced in our Fig. 8*A*. In this model, the signal coming from the semicircular canals projects onto the secondary vestibular neurones where it is combined with the output of a velocity storage element ($\dot{H}_{ok}$ in Fig. 8*A*) (Cohen, Matsuo & Raphan, 1977; Robinson, 1977; Raphan, Matsuo & Cohen, 1979) shared by the v.o.r. and the optokinetic system (Demer & Robinson, 1983). The signal then follows two parallel pathways: a direct one and another through a neural integrator (n.i.). The outputs of these two pathways are then combined and sent to the ocular plant. Fig. 8*D* and *E* shows the computed v.o.r. gains and phases (see Appendix) as a function of frequency under four conditions: (a) in the intact system, (b) with total failure of the velocity storage element, (c) with total loss of the n.i. and (d) when both $\dot{H}_{ok}$ and n.i. are lacking. This simulation predicts that the v.o.r. phase lead would be +93 deg at 0·10 Hz and +45 deg at 1 Hz, if the integrator n.i. is disabled. These values are close to those observed both in the cats with lesion of the p.h. region, including its rostral part and in the cat with m.v.n. lesion (Fig. 8*B* and *C*). By comparing Fig. 8*B* and *C* and Fig. 8*D* and *E*, it was concluded that the v.o.r. integrator processing was disturbed in these lesioned cats (cat 16, cat 19, cat 21 and cat 23). By contrast, the v.o.r. integrator was found to be roughly undisturbed in cats where the caudal four-fifths of the p.h. was completely destroyed (cat 18 and cat 26). The v.o.r. integrator was also relatively unaffected after posterior vermectomy (used for comparison). The n.i. was undisturbed by our mid-line lesions but it was possible that this type of lesion affected the velocity storage element. Such a perturbation would produce a mild phase advance. Indeed Fig. 7 (cat 27) shows a phase advance larger than in controls.

Electrolytic lesion experiments are always difficult to interpret, because it is not known whether the observed effect is due to the death of the neurones of the lesioned region or due to cutting the multiple passing fibres. In this respect, negative results are the most reliable with such lesion experiments. It is thus worth emphasizing that the integrator was intact while the caudal four-fifths of the p.h. nucleus was completely destroyed.

As far as our 'positive' results are concerned, we clearly demonstrated, for the first time, that Robinson's neural integrator was destroyed by a lesion placed 'in the region of' the rostral part of the p.h. nucleus. To know the respective responsibilities of the damaged p.h. neurones and of the cut passing fibres necessitates lesion experiments with kainic acid. This will be the aim of our future work.

Is the integration processing of the saccades affected by our lesions?

A saccade and the subsequent fixation are determined by the pulse-step firing of the ocular motoneurones (Robinson, 1964). The dynamics of eye movements are largely determined by the viscous and elastic elements of the extraocular muscles and of the globe-restraining tissues. These parameters were measured in the cat by Collins (1971) and a model was proposed. If a pulse signal without a concomitant step (that is in case of total failure of the saccadic integrator) is provided to orbital mechanics,

the resulting eye movement will be a saccade followed by a post-saccadic drift, with an exponential time constant of about 0·16 s (Goldberg, 1980). The saccadic integration processing was thus very seriously affected in cats 16, 19, 21 and 23 where the time constants of the observed post-saccadic drift were 0·34, 0·4, 0·8 and 0·6 s respectively; mildly disturbed in cats 18 (τ = 1·8 s) and 26 (τ = 2 s), and unaffected in cats 25, 27 and 28 (no post-saccadic drift).

The role of the commissural fibres in the v.o.r. integrator

Galiana & Outerbridge (1984) proposed a model in which the major part of the integration processing of the v.o.r. was due to the positive feed-back effect created by the reciprocal inhibitory commissural pathways between the vestibular nuclei (see Introduction). These authors pointed out in the discussion of their paper that the observations of Blair & Gavin (1981) and of De Jong, Cohen, Matsuo & Uemura (1980) on monkeys supported their model. We think such an argumentation is inappropriate. De Jong *et al.* (1980) showed that the optokinetic after-nystagmus (o.k.a.n.) was lost after mid-line section of the medulla from the obex to just behind the abducens nucleus. In our opinion, the loss of o.k.a.n. was due to the failure of the velocity storage element (yielding the $\dot{H}_{ok}$ signal in Fig. 8*A*), but not to any interference with the v.o.r. integrator, n.i. The results of our mid-line lesions argued in that direction. Indeed cat 27 with a mid-line cut in the medulla also showed a total loss of the o.k.a.n. (see the results described in the companion paper: Cheron, Gillis & Godaux, 1985); however, no phase advance was seen in the v.o.r., providing evidence of the integrity of the v.o.r. integrator in this case. The results of Blair & Gavin (1981) should be discussed in the same way. The velocity storage element is probably shared by the optokinetic system and the vestibulo-ocular system (Demer & Robinson, 1983). The cancellation of the $\dot{H}_{ok}$ signal can be correlated with a reduction of the time constant of the post-rotatory nystagmus to 4 s without any reduction of initial amplitude of the nystagmus. This was really observed by Blair & Gavin (1981). By contrast a failure of the v.o.r. integrator (n.i.) should strongly reduce both the amplitude and the time constant of the nystagmus.

Our results showed characteristic n.i. failure obtained with an electrolytic lesion in the region of the rostral p.h. behind the abducens nucleus. It could be argued that this defect was not due to the lesion of commissural passing fibres, since no similar defect was observed in case of commissural lesions on the mid line at the same level (cats 27 and 28). In spite of the fact that we probably did not cut all the vestibular crossing fibres, our experiments did not fit in with the model of Galiana and Outerbridge (1984).

Comparison with micro-electrode studies

The relation of the p.h. nucleus with the oculomotor and vestibular systems is now well established. Most of the neurones of the p.h. discharge during saccades and fixation, as well as during the v.o.r. and the optokinetic nystagmus (o.k.n.). The encoded variables are either the eye position or the eye position and velocity (Baker, Gresty & Berthoz, 1975; Lopez-Barneo, Ribas & Delgado-Garcia, 1981; Lopez-Barneo *et al.* 1982). These neurones were found throughout the rostrocaudal extension of the nucleus. The majority of the p.h. neurones are of the type II (Blanks,

Volkind, Precht & Baker, 1977; Hikosaka, Igusa & Imai, 1978). Furthermore, Gresty & Baker (1976) described in the rostral part of the nucleus some neurones sensitive to voluntary or passive displacements of the neck. What is the functional role of the p.h.? Two functional roles were hypothesized for the p.h. nucleus. (1) The fact that many p.h. neurones encode eye position, exclusively or partly, was often put forward to implicate the p.h. nucleus in v.o.r. integration processing (Lopez-Barneo, Darlot & Berthoz, 1979; Lopez-Barneo *et al.* 1982). (2) Berthoz and Baker's group (Lopez-Barneo *et al.* 1982) also pointed out that the prepositus nucleus could be implicated in eye–head co-ordination. They suggested that 'a question of future interest is whether the p.h. subserves a larger role in gaze than has now been shown for eye movement alone'. In view of our negative results after lesion of the caudal four-fifths of the p.h., it must be pointed out that the majority of the eye-position-related neurones found throughout the rostrocaudal extension of the p.h. nucleus are not implicated in the integration processing of the horizontal v.o.r.

Comparison with previous p.h. lesion experiments

In view of the abundant literature concerning micro-electrode studies in the p.h. nucleus, it is surprising that there is only one report of a p.h. lesion in the literature (Uemura & Cohen, 1973). These authors made a unilateral electrolytic lesion in the p.h. region of two monkeys. In each of the animals the lesion was about 1 mm in diameter and laid just behind the abducens nucleus, i.e. in the region we referred to in this paper as the rostral part of the p.h. Uemura & Cohen (1973) tested (1) spontaneous nystagmus, (2) optokinetic nystagmus, obtained by rotating a striped drum surrounding the animal, and (3) caloric nystagmus. They found (1) a gaze nystagmus when the animal attempted to look to each side, (2) the gain of the optokinetic nystagmus elicited toward the side contralateral to the lesion was dramatically decreased, (3) the direction of caloric nystagmus was not changed by lesions but there was directional preponderance to the ipsilateral side.

In our experiments, the lesions were bilateral and extended over about 4 mm in the rostrocaudal direction. From the correlation of the histological placements of the lesions with the 'negative' results of cats 18, 25 and 26 and the 'positive' results of cats 16, 19 and 21, we concluded that only the rostral part of the p.h. could be important in the horizontal gaze holding system and in the horizontal v.o.r. integration processing. This conclusion agrees with previous experiments (Uemura & Cohen, 1973) where the rostral pole of the p.h. was selectively destroyed.

The same authors found no spontaneous nystagmus, no major change of the o.k.n. and of the caloric nystagmus after lesion of the m.v.n. At first sight, there is some discrepancy between these negative results and ours. But the lesion carried out by Uemura & Cohen (1973) was localized in the external half of the rostral m.v.n. whereas our lesion was rather in the internal half of the m.v.n., in the region adjacent to the p.h.

Correlation with the neuroanatomical connexions

There are extensive connexions between the p.h. nucleus and nearly all of the brain-stem and cerebellar structures involved in oculomotor function (see McCrea, Baker & Delgado-Garcia, 1979) but some anatomical findings suggest that the

perihypoglossal complex may not work as a homogeneous functional unit (Kotchabhakdi, 1977; Alley, 1977; Graybiel, 1977; Yingcharoen & Rinvik, 1983). Therefore it is not surprising that lesions in different parts of the p.h. produce different effects.

In 1975, Robinson put forward the hypothesis of a final common integrator. Neuroleptics were recently described to affect differently the saccadic and the vestibular integrator (Godaux & Laune, 1983). The present lesions of the m.v.n. and p.h. have very similar effects on both the saccadic and the vestibular integrators. For facility, we wish to discuss the two integrators separately.

Studying the output of the vestibular nuclei in the m.l.f., Pola & Robinson (1978) concluded that the integration processing took place before the output from the v.n. As a corollary, the v.o.r. integrator n.i. must receive its input from primary or secondary vestibular afferents and must send its output to the m.v.n. Of course, such conditions can be filled by internal connexions within the v.n. Therefore integration may still be done within the v.n. (although it might need collaboration of the p.h.). But what about these conditions in the hypothesis of p.h. as the neural integrator? The v.n. does project to the p.h. (Baker & Berthoz, 1975*b*). But recently the extensive investigations of Carleton & Carpenter (1983) demonstrated that only cells in the caudal half of the prepositus projected to the m.v.n. Thus, following this paper, the rostral p.h. seems to be lacking the *sine qua non* connexion as a candidate for the neural integrator. Nevertheless, Carleton & Carpenter (1983) injected horseradish peroxidase only into the middle part of the m.v.n. By contrast, injecting horseradish peroxidase into the rostral part of the m.v.n., Balaban (1983) demonstrated a projection of the whole of the p.h. nucleus to the contralateral rostral m.v.n. Therefore no basic neuroanatomical data argue against the candidature of the rostral p.h. or of the v.n. as being the v.o.r. underlying structure.

Another possibility is that the integration processing is a result of interactions between the p.h. and the m.v.n. The v.n. projects to the p.h. (Baker & Berthoz, 1975*b*), and the p.h. projects back to the m.v.n. (Balaban, 1983). It is possible that a positive feed-back effect is created by these reciprocal relations. Such a positive feed-back effect could improve the effective integration function of a bad integrator located in the v.n.

To be a candidate for the neural integrator of the saccadic system, a structure has to receive the pulse input which is generated in the pontine paramedian reticular formation (p.p.r.f.; Keller, 1974). There is a strong connexion from the p.p.r.f. to the ipsilateral p.h. (Graybiel, 1977). Interestingly, this projection terminates more heavily in the rostral pole of the p.h. nucleus (Graybiel, 1977). The p.h. projects to the oculomotor nuclei both directly (Graybiel & Hartweig, 1974; Baker & Berthoz, 1975*a*) and indirectly via the m.v.n. (Balaban, 1983). The flocculus which is known to influence the gaze-holding system (Robinson, 1974; Westheimer & Blair, 1974; Godaux & Vanderkelen, 1984) was seen to project to the rostral part of the p.h. and not to the rest of the p.h. (Kotchabhakdi, 1977; Alley, 1977; Graybiel, 1977; Yingcharoen & Rinvik, 1983) while the reverse was observed for the vermis projections (Kotchabhakdi, 1977). Therefore no basic neuroanatomical data argue against the candidature of the rostral p.h. as being the saccadic integrator underlying structure.

In conclusion: where is (are) the integrator(s)?

Until now the proposed candidates for the integrator(s) underlying structure(s) are (1) the cerebellum, (2) the p.p.r.f., (3) the m.v.n., (4) the p.h. and (5) the vestibular internuclear commissural pathway (see Introduction).

After cerebellectomy, the observed post-saccadic drift has a time constant of about 1·3 s (Robinson, 1974; Godaux & Vanderkelen, 1984). The measured phase advance of the v.o.r. is of +50 deg at 0·10 Hz (Keller & Precht, 1979; Godaux & Vanderkelen, 1984). These modifications are too small to imagine that the cerebellum could be the location of the integrator(s). The cerebellum influences the integrator(s) which is (are) elsewhere. A recent work of Henn, Lang, Hepp & Reisine (1984) eliminates the candidature of the p.p.r.f. After a bilateral lesion of the p.p.r.f. by kainic acid the eyes could still hold eccentric positions (achieved by a pursuit movement), and no phase advance of the v.o.r. was observed.

From the present work, it can be concluded that the integrator(s) could be located in the rostral p.h. or in the m.v.n., but not in the posterior four-fifths of the p.h. It is also suggested from our mid-line lesions that the vestibular commissural pathway is an unlikely candidate.

APPENDIX

The v.o.r. pathway consists of three main parts: the semicircular canals, the central neuronal network and the ocular plant (Fig. 8*A*).

In Laplace transform notation, the transfer function of the canals is

$$s \cdot \frac{sT_c}{(sT_c+1)} \cdot \frac{sT_a}{sT_a+1} \cdot (sT_z+1), \tag{1}$$

where T_c and T_a are the cupula time constant and the adaptive time constant respectively. (sT_z+1) is related to the fact that, above a certain frequency, the discharge of the primary vestibular afferents becomes more proportional to head acceleration than to head velocity. The values of the foregoing parameters are $T_c = 4$ s (in the cat), $T_a = 80$ s and $T_z = 0{\cdot}049$ s. When working in the frequency range from 0·05 to 1 Hz (in view of the values of T_a and T_z), a good approximation of (1) is given by

$$s \cdot \frac{sT_c}{(sT_c+1)}. \tag{2}$$

The first step in central processing is to increase the time constant of the signal coming from the cupula. This velocity storage takes place in the vestibular nucleus. In Laplace transform notation, it can be approximated by substituting T_c by $T_{v.o.r.}$ in relation (2). $T_{v.o.r.} = 12$ s in the cat. Notice that v.o.r. cannot strictly be represented by a single time constant (see eqn. (7) of Cheron *et al.* 1985). Nevertheless, it is a justifiable approximation in the considered range (0·05–1 Hz).

In the next step, the velocity signal is processed by both an integrating pathway (s_0/s) and a direct pathway of gain k_{e1}. The sum of these pathways may thus be written as $s_0(1/s + k_{e1}/s_0)$. Let us point that the time constant T_{e1} characterizing

the plant dynamics does not influence the experimental results. It is therefore assumed that $k_{e1}/s_0 = T_{e1}$, in order to compensate the plant dynamics.

The factor s_0 is included in a general gain term g (see bottom). This step may thus finally be taken into account as

$$\frac{1}{s}(1+sT_{e1}). \tag{3}$$

The transfer function of the plant is

$$\frac{e^{-s\tau}}{(sT_{e1}+1)(sT_{e2}+1)}, \tag{4}$$

where $T_{e1} = 0{\cdot}16$ s; $T_{e2} = 0{\cdot}016$ s and $\tau = 0{\cdot}008$ s.

All scale factors have been replaced in Robinson's (1977, 1981) model by one, equivalent net gain ($-g$) which is about 0·9. Therefore the transfer function of the whole v.o.r. is

$$-g.s.\frac{sT_{v.o.r.}}{sT_{v.o.r.}+1}\cdot\left(T_{e1}+\frac{1}{s}\right)\cdot\frac{e^{-s\tau}}{(sT_{e1}+1)(sT_{e2}+1)} \tag{5}$$

or, after simplification,

$$-g\cdot\frac{sT_{v.o.r.}}{sT_{v.o.r.}+1}\cdot\frac{e^{-s\tau}}{sT_{e2}+1}\cdot \tag{6}$$

In the frequency range 0·05–1 Hz, a good approximation of eqn. (6) is given by

$$H(s) = -g\cdot\frac{sT_{v.o.r.}}{sT_{v.o.r.}+1}\cdot e^{-s\tau}. \tag{7}$$

This latter expression is used (in simulation displayed in Fig. 8*D* and *E*) as the transfer function of the v.o.r. in the normal cat.

From the above considerations, it is clear that suppressing the velocity storage element ($\dot{H}_{ok}$) amounts to substituting $T_{v.o.r.}$ by T_c in eqn. (7).

$$H(s) = -g\frac{sT_c}{sT_c+1}\cdot e^{-s\tau} \tag{8}$$

gives the transfer function of the v.o.r. when $\dot{H}_{ok}$ is disabled.

Suppressing the neural integrator n.i. in the model amounts to suppressing the $1/s$ term in eqn. (5). This latter becomes

$$-g\cdot s\cdot\frac{sT_{v.o.r.}}{sT_{v.o.r.}+1}\cdot T_{e1}\cdot\frac{e^{-s\tau}}{(sT_{e1}+1)(sT_{e2}+1)} \tag{9}$$

which can be approximated by (see above)

$$H(s) = -g\frac{sT_{v.o.r.}}{1+sT_{v.o.r.}}\cdot\frac{sT_{e1}}{1+sT_{e1}}\cdot e^{-s\tau}. \tag{10}$$

This expression gives the transfer function of the v.o.r. when the neural integrator is disabled.

When both the n.i. and the $\dot{H}_{ok}$ processings are disabled, the corresponding transfer function is

$$H(s) = -g \cdot \frac{sT_c}{1+sT_c} \cdot \frac{sT_{e1}}{1+sT_{e1}} \cdot e^{-s\tau}. \quad (11)$$

Transfer functions (7), (8), (10) and (11) were used to compute the gain and phase of the response to a sinusoidal input. The computed values are plotted in Fig. 8*D* and *E*.

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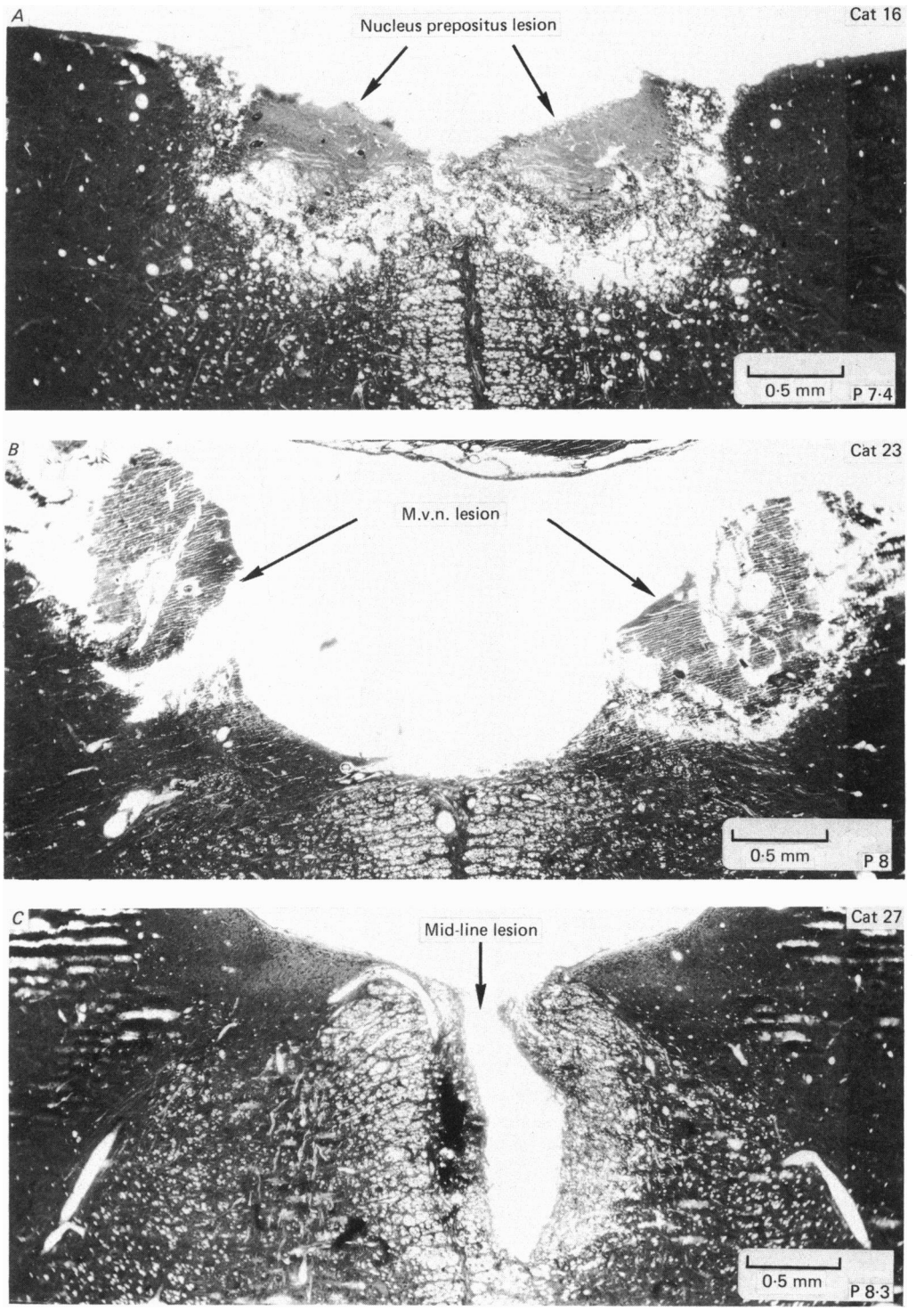
EXPLANATION OF PLATE

Photographs illustrating the three types of electrolytic lesion made in this paper. *A*, bilateral p.h. nuclei lesion in cat 16. Photograph of the histological section in the vertical stereotactic plane through the level P 7·4. *B*, bilateral m.v.n. lesion in cat 23. Histological section through the level P 8·2. *C*, mid-line lesion in cat 27. Histological section through the level P 8·3.


A
Nucleus prepositus lesion
Cat 16
0·5 mm
P 7·4
B
M.v.n. lesion
Cat 23
0·5 mm
P 8
C
Mid-line lesion
Cat 27
0·5 mm
P 8·3

(*Facing p.* 94)