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DISABLING OF THE OCULOMOTOR NEURAL INTEGRATOR BY KAINIC ACID INJECTIONS IN THE PREPOSITUS–VESTIBULAR COMPLEX OF THE CAT

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SUMMARY

1. This study was intended to test the candidature of the prepositus–vestibular nuclear complex for being the location of the oculomotor neural integrator (Robinson's integrator).

2. Microinjections of kainic acid (2 μg dissolved in 1 μl) were made in awake cats. Injection sites were located either in the prepositus hypoglossi nucleus (p.h.), the medial vestibular nucleus (m.v.n.), the medial longitudinal fasciculus (m.l.f.) or in the magnocellular tegmental field of the reticular formation.

3. Theory predicts that a complete disabling of the neural integrator will cause (a) an exponential post-saccadic drift whose time constant will be 0·16 s in the dark (b) a phase lead of +93 deg as the vestibulo-ocular reflex is tested at 0·10 Hz in the dark and (c) a nearly complete abolition of the optokinetic nystagmus (o.k.n.).

4. About 1 h after a unilateral kainic acid injection in the p.h., we observed (a) a large bilateral post-saccadic drift (time constant sometimes as low as 0·2 s) (b) a large phase lead at 0·10 Hz (range: from +69 to +98 deg) (c) an abolition of the o.k.n. Control injection of phosphate buffer in the p.h. did not produce any deficit.

5. A unilateral kainic acid injection in the m.v.n. induced a nystagmus followed by signs of bilateral failure of the neural integrator similar to those observed after kainic acid injection in the p.h.

6. Injection near the mid-line, between the two p.h. nuclei, induced a defect of the neural integrator less than that observed after kainic acid injection in either the p.h. or the m.v.n. Injection of kainic acid in the magnocellular tegmental field of the reticular formation did not produce any sign of failure of the neural integrator. No post-saccadic drift was observed.

7. We have concluded that (a) the p.h. nucleus is involved in the integration processing, and that (b) the m.v.n. is involved either in the integration processing or in the relaying of the output of the neural integrator to the oculomotoneurones.

INTRODUCTION

Neurophysiologists working in the field of eye movements agree about the existence of a neural integrator (in the mathematical sense of the word) whose functioning is necessary for generating correct saccades, correct vestibulo-ocular

reflex and correct optokinetic response (see Robinson, 1981; see also the introduction in Cheron, Godaux, Laune & Vanderkelen, 1986). This integration processing should generate the gaze-holding signal from the saccadic-movement signal (the pulse) provided by the pontine paramedian reticular formation (p.p.r.f.) (Keller, 1974); it should also supply a position signal from the velocity signal originating from either the semicircular canals (Skavenski & Robinson, 1973) or the retina (Cohen, Matsuo & Raphan, 1977). All three integration processings should be done by a common final integrator (Robinson, 1975, 1981), although some doubt subsists (Godaux & Laune, 1983).

The hypothesis of the neural integrator was proposed by Robinson in 1971 (Robinson, 1971). Despite a 15 year appreciation of its reality, its anatomical location has been elusive. This paper is devoted to the question of the location of the oculomotor neural integrator. There are five candidates for being the underlying structure of the integrator: (1) the cerebellum (Carpenter, 1972), (2) the p.p.r.f. (Cohen & Komatsuzaki, 1972), (3) the medial vestibular nucleus (m.v.n.) (Robinson, 1975), (4) the prepositus hypoglossi (p.h.) nucleus (Lopez-Barneo, Darlot, Berthoz & Baker, 1982) and (5) the commissural pathway binding the two vestibular nuclei (Galiana & Outerbridge, 1984). The candidatures of the cerebellum and of the p.p.r.f. have been ruled out respectively by Robinson (1974) and by Henn, Lang, Hepp & Reisine (1984). Recently, at about the same time and independently, two research groups undertook to test the candidature of the prepositus–vestibular nuclear complex: ours on cat (Godaux, Cheron & Sasserath, 1985; Cheron *et al.* 1986; Cheron, Gillis & Godaux, 1986) and that of Robinson on monkey (Cannon & Robinson, 1985).

In our preceding work we found signs of failure of the neural integrator after electrolytic lesions made either in the p.h. or in the m.v.n., but electrolytic lesions destroy both the neurones located at the site of the lesion and the fibres of passage. On the other hand, our previous lesions were performed just after surgical ablation of the vermis under general anaesthesia, so that we were able to look for possible effects of the lesions only 3 days after the operation. This experimental procedure could lead us to overlook possible transient defects. To avoid either disadvantages in the present work, we injected kainic acid in the p.h.–m.v.n. complex of awake cats. Kainic acid is well known to act only on neurones while sparing fibres of passage (Coyle, Molliver & Kuhar, 1978; McGeer, Olney & McGeer, 1978). Monitoring of eye movements during kainic acid injection allowed us to detect pathological movements induced even very transiently.

Our results support the candidature of the p.h.–m.v.n. complex for being the underlying structure of the integrator. Preliminary accounts of the experiments described here were given at the tenth European Neuroscience Congress held in Marseille in September 1986 (Godaux, Cheron & Baras, 1986).

METHODS

General procedure

Experiments were performed on eight cats. Under general anaesthesia (xylidino-dihydrothiazin, Rompun, Bayer, 3 mg/kg, and pentobarbitone, Nembutal, Abbott, 20 mg/kg) and aseptic conditions three devices were chronically implanted. (1) A scleral search coil was implanted

subconjunctivally in one eye (Judge, Richmond & Chu, 1980). (2) A stainless-steel chamber, 10 mm in diameter, was stereotaxically placed so that its centre was above the genu of the facial nerve. (3) Two transverse tubes were placed on the skull in the horizontal plane and embedded in dental acrylic cement, in order to immobilize the head during the experiments.

About 1 week later the cats were loosely restrained in a body box to which the head was fixed.

A further week later glass-covered tungsten microelectrodes were introduced through the cylinder and used to explore the medulla by cathodal microstimulations. Impulses trains (200/s, 0·5 ms shock duration) were used. The current varied between 3 and 50 μA. In order to determine the position of the genu of the facial nerve, we looked at the face of the animal during the microstimulations. In order to identify the position of the abducens, prepositus and medial vestibular nuclei, we monitored eye movements in light and in darkness during microstimulations.

At the end of this session of search for guide marks, the position of the target for the microinjection of kainic acid (prepositus nucleus or medial vestibular nucleus) was selected. Control records of the eye movements were performed the day before the microinjection of kainic acid. Each cat received one or two microinjections at 8-day intervals. Animals were tested on a daily basis.

After an additional survival time of 2 weeks (after the second injection), small cathodal electrolytic lesions (10 μA, 10 s) were performed at selected sites in order to aid in the reconstruction of injection sites. After that, the animals were perfused (see below).

Eye movement recording

Eye movements were measured using the magnetic field–search coil technique (Fuchs & Robinson, 1966). Our device was fitted with only an horizontal magnetic field. The eye movement measurement system has a bandwidth of 0·1–1000 Hz and a sensitivity of 0·25 deg. Calibration was obtained by keeping the untrained cat (in a body box to which the head was fixed) stock-still in space while the surrounding magnetic field was rotated sinusoidally in the horizontal plane (Robinson, 1976). A relatively high frequency (1 Hz) was used in order to increase the probability of obtaining cycles devoid of unwanted spontaneous saccades.

Eye movement tests

We observed (1) the horizontal saccades in light and in darkness, (2) the horizontal vestibulo-ocular reflex (v.o.r.) in darkness and (3) the horizontal optokinetic nystagmus (o.k.n.). Alertness of the cat was maintained by intramuscular injection of amphetamine (0·5 mg/kg) or by production of strange sounds.

In order to elicit the v.o.r., the head of the cat was put in the centre of a turntable and placed so that the horizontal semicircular canals were about horizontal (nose 20 deg down). The head was submitted to either a sinusoidal movement ($\pm$20 deg; 0·05–1 Hz) or to a rotation at a constant velocity of 16 deg/s. The slow cumulative eye position curves were constructed manually from the raw records (Meiry, 1966). Gain was defined as the ratio of peak-to-peak eye position to peak-to-peak rotating frame position. Phase shift was designated as zero when eye and head movements were exactly opposite. Five to ten cycles were used.

The turntable was surrounded by a drum (1 m diameter, 1 m high) the inner wall of which was covered with alternating white and black stripes (10 deg each). O.k.n. was assessed during rotation of the drum at a constant velocity of 30 deg/s during 30 s. The animal was plunged into darkness before and after optokinetic stimulation. The o.k.n. and o.k.a.n. (optokinetic after-nystagmus) were analysed by measuring the velocity of the slow phases, once each second.

Kainic acid microinjections

Chemical lesions were produced with kainic acid (Coyle *et al.* 1978; McGeer *et al.* 1978). It was concentrated to 2 μg/μl, was dissolved in 0·2 M-phosphate buffer, and had a pH of 7·4. A glass micropipette was advanced through a guide tube (the same as that used for microstimulations). Injections of kainic acid were made using micropipettes and an air pressure delivery system. The tip of the glass micropipette was bevelled. Its other extremity was connected to a 5 ml syringe by a polyethylene tube. Air-tightness of the junctions of the system was achieved using thermoretractile sheaths. Only the micropipette was filled with kainic acid. Pulses of air were delivered manually while the meniscus level in the micropipette was monitored through a 12·5 ×

microscope. An initial pulse of 1/8 μl was injected at time zero. Additional pulses of 1/16 μl were delivered every 2 min from time 5 min to 31 min. The total amount of this injection by steps was 1 μl. During the injection, the animal was on the turntable and spontaneous eye movements (nystagmus and saccades) were monitored in the light.

Histological identification of lesion sites

Under deep pentobarbitone anaesthesia, the animals were perfused via the aorta first with 250 ml of saline and then with 1 l of 10% neutral-buffered formalin. Serial sections of 20 μm thickness cut from the medulla and pons were mounted on glass slides and alternately stained for cell bodies with cresyl violet and for myelin with luxol fast blue. The location of injection sites was determined through the histologic reconstruction of the micropipette penetration tracts with respect to the small electrolytic lesions.

RESULTS

The syndrome of the neural integrator failure

To validate the results, it is necessary to know the characteristics of the pathological eye movements which would be generated in case of complete failure of the neural integrator. These pathological movements can be predicted by using the Robinson models (Robinson, 1981) summarized in Fig. 1.

If the integration processing is missing in the saccadic system, the only signal to be passed on to the oculomotoneurones is a pulse. The resulting saccade will not be followed by a gaze-holding period but by an exponential post-saccadic drift with a time constant of about 0·16 s (Goldberg, 1980).

The v.o.r. can be assessed by a frequency analysis. By using Robinson's model (Fig. 1*B*), it can be predicted that a total failure of the neural integrator would cause both a reduction of the gain and a phase lead, especially at lower frequencies (see Fig. 8*D* and *E* in Cheron *et al.* 1986). In the just-quoted paper we computed that in the dark at 0·10 Hz, the v.o.r. phase lead would be +93 deg and the gain 0·10. In the normal cat, at 0·10 Hz, the v.o.r. phase lead is +10 deg and the gain about 0·9 (Cheron *et al.* 1986).

The v.o.r. can also be assessed by a velocity-step test. The pulse of head acceleration ($\Delta\ddot{h}$) is converted by the semicircular canal into a velocity-step signal ($\Delta\dot{h}$). In case of total failure of the neural integrator, the step signal ($\Delta\dot{h}$) is sent to the plant only through the direct pathway whose gain is gT_{e1} (where $g = 0{\cdot}9$ and $T_{e1} = 0{\cdot}16$ s). The resulting eye movement would be a step change (and not a ramp change) in eye position. For a constant velocity of head rotation of 16 deg/s, the predicted eye deviation would be as small as:

$$\Delta e = \Delta h g T_{e1} = 2{\cdot}3 \text{ deg}.$$

Using Robinson's model (1977, 1981) of the optokinetic system (Fig. 1*C*), it can be predicted that the optokinetic response would be nearly completely abolished if the integration processing is missing. In such a case, the velocity of the eye movement induced by a constant-velocity rotation of the surround at 30 deg/s would reach a maximum of only 3 deg/s after 0·6 s and would become as small as 0·3 deg/s after 20 s (see Appendix). Using the same model and the same values for the parameters, the maximal eye velocity of the normal response to the same optokinetic stimulus is predicted to be 25·5 deg/s.

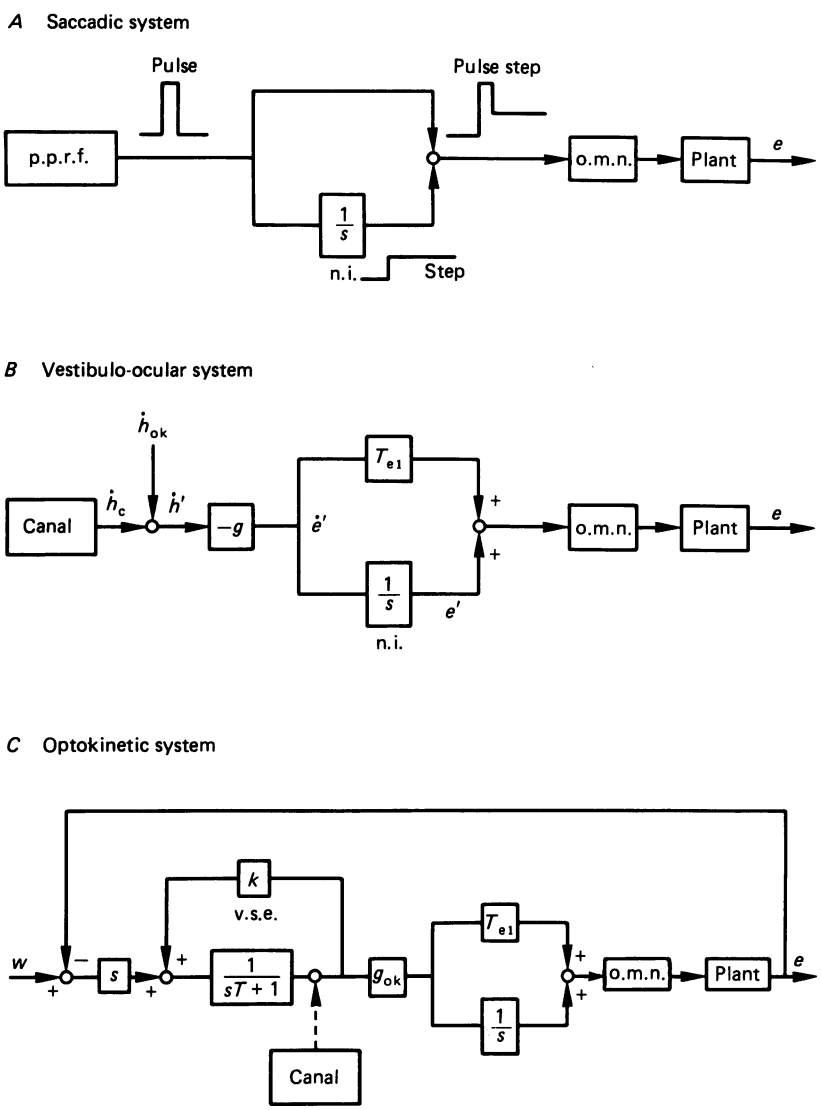

Fig. 1. *A*, Robinson's model (Robinson, 1971, 1975) of the saccadic system. P.p.r.f., paramedian pontine reticular formation; n.i., neural integrator; o.m.n., oculomotoneurones; e, eye position signal; $1/s$, transfer function of the neural integrator in Laplace transform notation. *B*, Robinson's model (Robinson, 1977, 1981) of the horizontal vestibulo-ocular reflex. Canal, the horizontal semicircular canal; $\dot{h}_c$, head velocity as coded by the semicircular canals; $\dot{h}_{ok}$, the central signal that increases the time constant of the signal originating from the canals; $-g$, overall reflex gain; T_{e1} is a time constant linked to the gain of the direct pathway; e, eye position signal. *C*, Robinson's model (Robinson, 1977, 1981) of the optokinetic system. w, world (surrounding) position; s, transfer function of a differentiator in Laplace transform notation; v.s.e., velocity storage element (Cohen *et al.* 1977). The v.s.e. is formed by a leaky integrator $(1/sT+1)$ and a positive feed-back loop, the gain of which is k. The overall reflex gain is g_{ok}. This sketch also indicates the place where the vestibular input from the semicircular canal (Canal) is combined with the optokinetic signal.

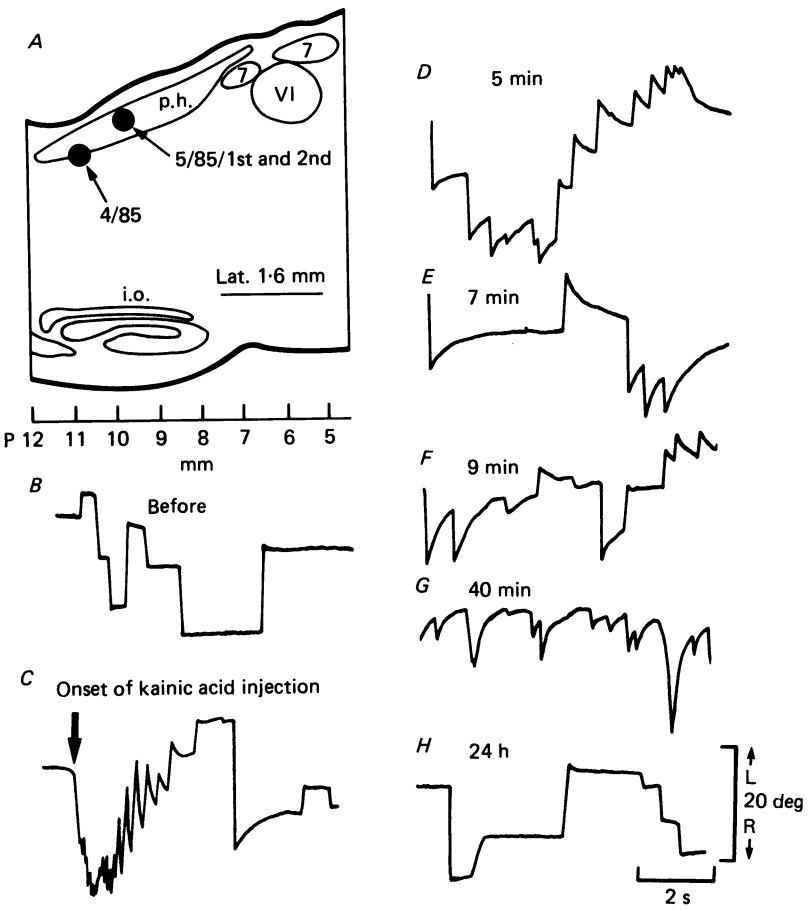

Fig. 2. Effect of kainic acid injection in the prepositus hypoglossi nucleus (p.h.) on saccades in light. *A*, location of the three injections of kainic acid in the prepositus hypoglossi nucleus 7, genu of the facial nerve; VI, nucleus of the sixth nerve; i.o., inferior olive. Large points indicate the injection sites. Injections are identified by the running number of the cat followed either by 1st (first) or 2nd (second) if two injections were performed in the same cat, or by nothing if only one injection was performed. *B–H*, spontaneous saccades in light before (*B*) and at various times (*C–H*) after the start of unilateral kainic acid injection in the right p.h. of cat 5/85 (first injection). *C*, transient nystagmus induced by the first pulse of kainic acid. *D–F*, bilateral gaze–paretic nystagmus. *G*, notice the large exponential post-saccadic drift of the left-directed saccades (time constant: about 0·2 s). *H*, recovery after 24 h.

A possible post-saccadic drift in the dark can be corrected in the light by the optokinetic system. As a result, the post-saccadic drift in the dark is never smaller than the post-saccadic drift in the light. This has to be pointed out as our procedure of injection (watching the meniscus during the repetitive injections of pulses of kainic acid) prevented us from monitoring the saccades in the dark during the first 31 min after starting the injection.

Kainic acid injections in the prepositus hypoglossi nucleus

Three injections of kainic acid were made in the p.h. nucleus, two at the same site 1 week apart in cat 5/85 and one in cat 4/85. The Nissl-stained sections showed apparently no permanent structural change. This fact obliged us to determine each injection site with respect to two small electrolytic lesions performed 1 and 2 mm below it. The location of the injection sites in the p.h. nucleus is shown in Fig. 2*A*.

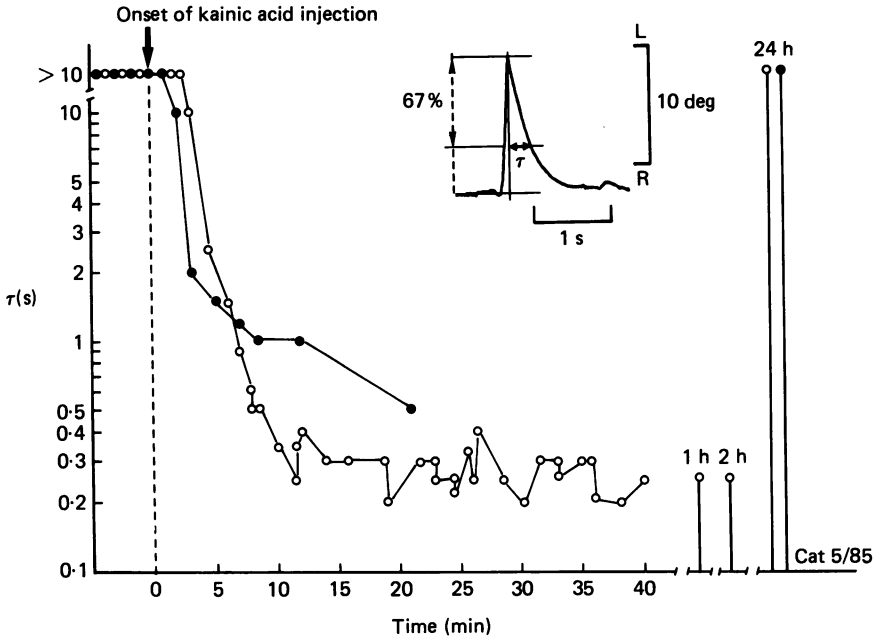

Fig. 3. Time constant of the spontaneous saccades (ordinate) in light as a function of the time (abscissa) after the start of unilateral kainic acid injection in the right p.h. (first injection in cat 5/85; see Fig. 2*A* for location). ●, left-directed saccades. ○, right-directed saccades. In insert, display of the method of measurement of the time constant (τ) of the post-saccadic drift.

The three injections modified eye movements in similar ways. We will use especially the case of the first injection in cat 5/85 to illustrate these effects.

Figure 2 shows spontaneous saccades in the light before (Fig. 2*B*) and at various times after the start of kainic acid injection (Fig. 2*C–H*). Injection of the first pulse of kainic acid induced an ipsilateral rapid deviation of the gaze followed by a transient nystagmus lasting about 3–4 s (Fig. 2*C*). During the subsequent 3 min there was neither abnormal saccades nor any deviation of the neutral point of the gaze. A bilateral centripetal post-saccadic drift was detected from the 3rd minute on. The time constant of the exponential drift dropped progressively for the saccades in both directions as shown in Figs 2 and 3. After the 20th minute, the cat no longer made saccades to the contralateral side. After 40 min, the time constant of the post-saccadic drift of the saccades directed to the ipsilateral side was about 0·2 s both in the light and in the dark. The saccades were normal the day after the injection.

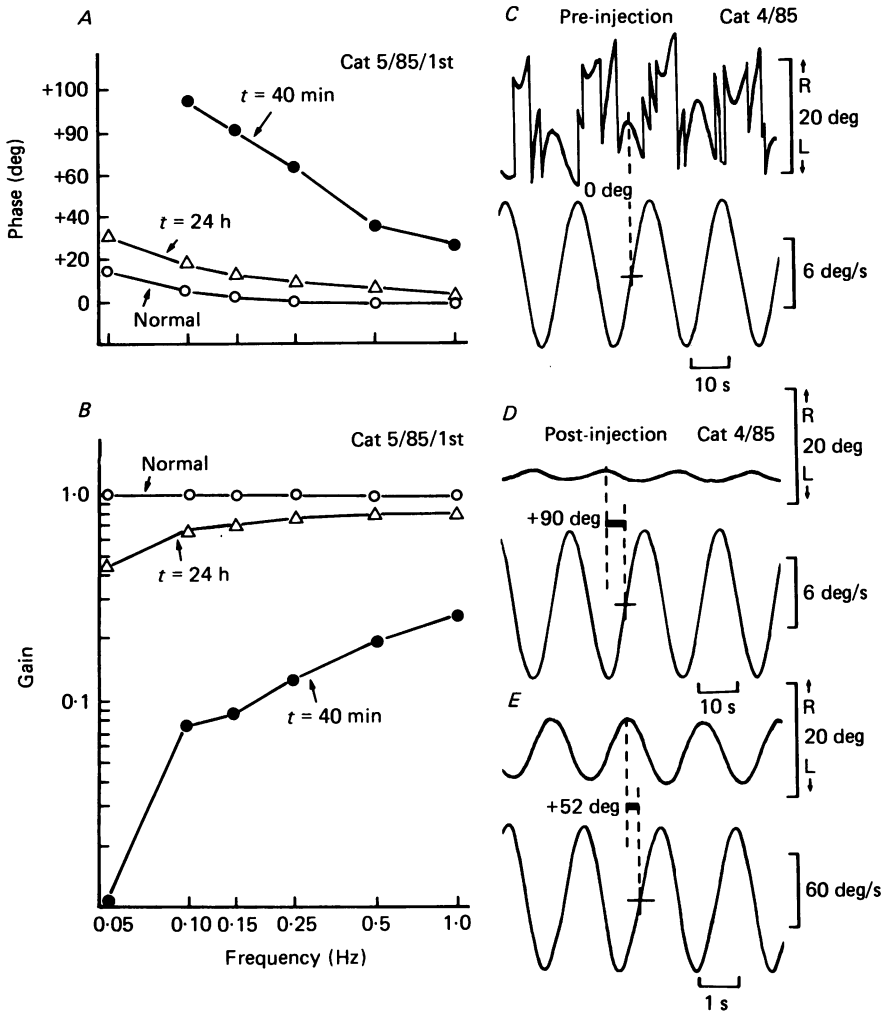

Fig. 4. *A* and *B*, diagram of the phase and gain of the v.o.r. tested in the dark before (○), 40 min after (●) and 24 h after (△) the start of unilateral kainic acid injection in the p.h. of cat 5/85 (first injection). *C*, v.o.r. of cat 4/85 tested in the dark before kainic acid injection at 0·05 Hz with a ±20 deg amplitude. The upper trace is the eye position signal whereas the lower trace is the head velocity signal, so that a possible phase advance has to be assessed by measuring the phase between the maxima of the reconstructed sinusoidal eye movement and the intercepts of the sinusoidal head velocity signal with the time axis. *D* and *E*, v.o.r. of cat 4/85 tested in the dark after kainic acid injection in the right p.h. (see Fig. 2*A*) at 0·05 Hz (*D*) and at 0·5 Hz (*E*).

The v.o.r. was tested between the 40th and the 60th minute. Gain and phase of the v.o.r. in the dark were seriously affected. There was a decrease of the gain and an increase of the phase lead especially at lower frequencies. Figure 4*A* and *B* shows the Bode plot before, 40 min after and 24 h after the start of kainic acid injection. Forty minutes after the start of kainic acid injection the gain and the phase lead at 0·10 Hz were respectively 0·06 and +93 deg. Figure 4*C* and *D* illustrates the v.o.r. before

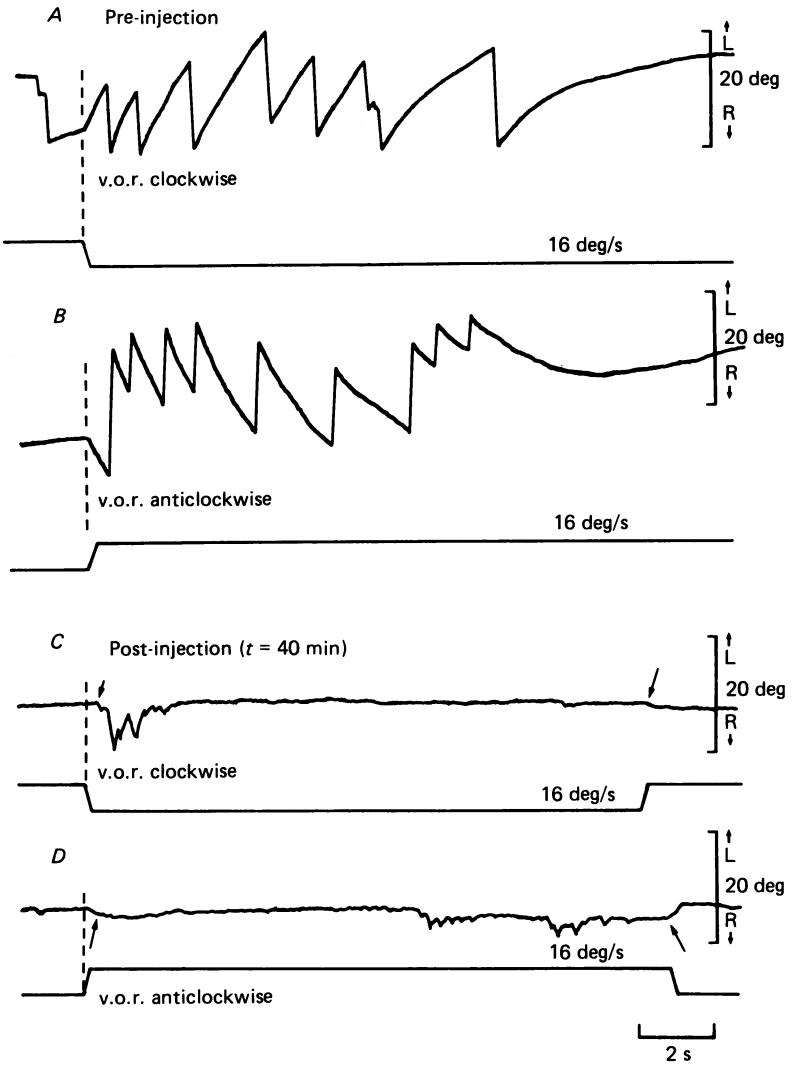

Fig. 5. Vestibulo-ocular reflex (v.o.r.) in response to a rotation of the head at a constant velocity of 16 deg/s. The v.o.r. was tested in the dark, clockwise and anticlockwise, before (*A* and *B*) and after (*C* and *D*) kainic acid injection in the right p.h. of cat 5/85 (first injection). Notice the small step change in eye position (arrows in *C* and *D*) instead of the ramp movement seen in the control records (*A* and *B*).

and after kainic acid injection in the right p.h. nucleus of cat 4/85. In each block (*C*, *D* or *E*) the upper trace is the eye position whereas the lower is the head velocity, so that a possible phase advance has to be assessed by measuring the phase between the maxima of the reconstructed sinusoidal eye movement and the intercepts of the sinusoidal head velocity signal with the time axis. In this case, the phase advance of the v.o.r. tested at 0·10 Hz was 0 deg before (Fig. 4*C*) and 90 deg after (Fig. 4*D*) kainic acid injection.

Before the injection, the gaze movement induced by a 16 deg/s constant rotation

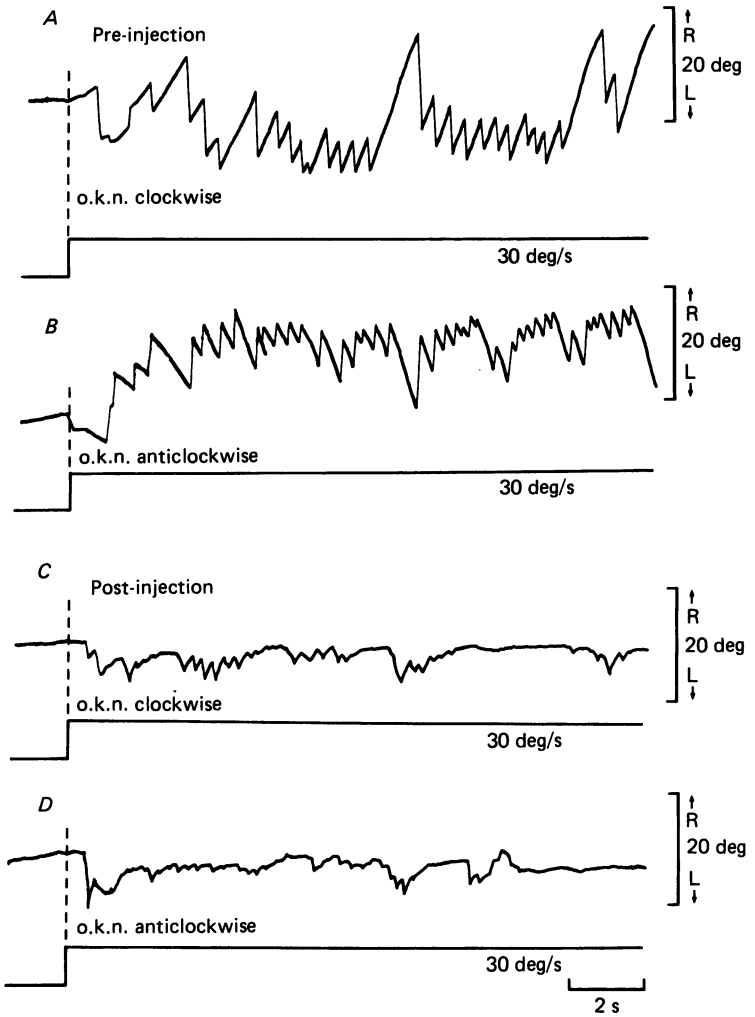

Fig. 6. Optokinetic response to a step of velocity of 30 deg/s before (*A* and *B*) and after (*C* and *D*) kainic acid injection in the right p.h. of cat 5/85 (first injection). O.k.n. was tested clockwise (*A* and *C*) and anticlockwise (*B* and *D*).

of the turntable was a ramp (Fig. 5*A* and *B*). Forty minutes after the injection, the same stimulus elicited only a small step deviation. The change in eye position was 0·6 deg when the head of the cat rotated towards the injection site (clockwise rotation) (Fig. 5*C*) and 2 deg when it rotated in the direction opposed to the injection site (anticlockwise rotation) (Fig. 5*D*). The arrows in Fig. 5*C* and *D* point to these small changes in eye position.

The optokinetic response tested 1 h 30 min after the onset of kainic acid injection was virtually abolished in both directions (clockwise and anticlockwise). Figure 6 compares the optokinetic response before (*A* and *B*) and after (*C* and *D*) kainic acid injection. Maximal velocity of the slow phases dropped from 20 deg/s to about

0 deg/s in the clockwise direction and from 22 deg/s to again about 0 deg/s in the opposite direction.

As shown in Tables 1–3, the two other injections in the p.h. nucleus modified eye movements in similar ways. It is interesting to point out that injection of kainic acid in a location submitted to kainic acid toxic effect 1 week before produced again effects similar to those observed after the first injection (see cat 5/85, first and second injections in Tables 1–3).

TABLE 1. Post-saccadic drift of the saccades in the light after injections of kainic acid or phosphate buffer. Values in parentheses are related to saccades recorded in darkness. Bars correspond to unavailable measurements

	Minimal time constant of the ipsilateral saccades (s)	Minimal time constant of the contralateral saccades (s)	Delay for a post-saccadic drift to be detectable (min)
Kainic acid injection in the p.h.:			
cat 5/85 – first injection	0·2 (0·2)	0·3 (—)	3
cat 5/85 – second injection	0·2 (0·2)	0·5 (0·3)	3
cat 4/85 – only injection	0·2 (—)	0·4 (—)	4
Kainic acid injection in the m.v.n.:			
cat 1/86 – only injection	0·2 (—)	0·4 (—)	9
cat 2/86 – second injection	0·5 (—)	0·2 (0·2)	31
cat 3/86 – second injection	0·15 (0·15)	0·5 (0·5)	12
cat 5/86 – only injection	0·3 (0·2)	0·7 (—)	17
cat 6/86 – second injection	0·2 (0·2)	0·3 (0·3)	6
cat 2/86 – first injection	3·0 (—)	3·0 (—)	60
Kainic acid injection out of the p.h.–m.v.n. complex:			
cat 3/86 – first injection	1·0 (0·8)	0·8 (0·7)	15
cat 6/86 – first injection	1·0 (0·5)	3·0 (0·8)	18
cat 1/87 – third injection	No detectable post-saccadic drift		
Phosphate buffer injection in the p.h.:			
cat 1/87 – first injection	No detectable post-saccadic drift		
cat 1/87 – second injection	No detectable post-saccadic drift		

Kainic acid injections in the medial vestibular nucleus

Six kainic acid injections were made in different regions of the m.v.n. in five cats (see Fig. 7). One of them (cat 2/86, first injection) was performed very near to the floor of the 4th ventricle (Fig. 7*D*).

Except for the first injection in cat 2/86, the injections in the m.v.n. induced similar pathological movements. We will use the case of the second injection in cat 2/86 to illustrate these effects (Fig. 8).

The first abnormal eye movement detected after the injection was a nystagmus, the slow phases of which were linear (and not exponential). This nystagmus appeared on the 8th minute after starting the injection and vanished on the 30th minute. Its slow phases were directed first to the side opposite to that of the injection, and then, after a pause of the nystagmic pattern (from 8th to 11th minute), to the side of the injection (Fig. 8*C*). A bilateral post-saccadic drift was also observed from the 31st minute (Fig. 8*D–F*). Complete recovery was achieved within 48 h (Fig. 8*G–I*).

The v.o.r. was also seriously disrupted. A velocity step of head rotation did not

TABLE 2. Gain and phase of the vestibulo-occular reflex (v.o.r.) measured at 0·1 Hz before and after injections of kainic acid or phosphate buffer. Bars correspond to unavailable measurements

	Gain		Phase (deg)	
	Before	After	Before	After
Kainic acid injection in the p.h.:				
cat 5/85 – first injection	1·02	0·06	+5	+93
cat 5/85 – second injection	0·95	0·09	+9	+98
cat 4/85 – only injection	1·00	0·16	0	+69
Kainic acid injection in the m.v.n.:				
cat 1/86 – only injection	0·92	0·08	+10	+80
cat 2/86 – second injection	1·03	0	0	—
cat 3/86 – second injection	1·11	0·13	+1	+90
cat 5/86 – only injection	1·19	0	0	—
cat 6/86 – second injection	1·04	0·10	+5	+90
cat 2/86 – first injection	1·01	0	+6	—
Kainic acid injection out of the p.h.–m.v.n. complex:				
cat 3/86 – first injection	1·12	0·4	0	0
cat 6/86 – first injection	1·10	0·2	+6	0
cat 1/87 – third injection	0·89	—	+8	+17
Phosphate buffer injection in the p.h.:				
cat 1/87 – first injection	0·90	0·85	+7	+8
cat 1/87 – second injection	0·92	0·90	+10	+11

TABLE 3. Maximum eye velocity achieved during the optokinetic nystagmus (o.k.n.) induced by a step of velocity (30 deg/s and 30 s duration), before and after injection of kainic acid or phosphate buffer. Each value is the mean of four measurements. Bars correspond to unavailable measurements

	Optokinetic stimulation directed towards the side of the injection		Optokinetic stimulation directed towards the side opposite to that of the injection	
	Before (deg/s)	After (deg/s)	Before (deg/s)	After (deg/s)
Kainic acid injection in the p.h.:				
cat 5/85 – first injection	22·0±3·0	0	22·0±3·3	0
cat 5/85 – second injection	22·6±1·5	0	21·3±2·6	0
cat 4/85 – only injection	25·0±2·0	0	22·0±1·6	0
Kainic acid injection in the m.v.n.:				
cat 1/86 – only injection	25·0±3·1	0	24·0±5·2	0
cat 2/86 – second injection	31·0±3·2	0	30·0±3·1	0
cat 3/86 – second injection	25·6±4·0	0	28·6±1·2	0
cat 5/86 – only injection	21·6±2·1	0	20·8±1·3	0
cat 6/86 – second injection	23·0±1·2	0	26·0±2·3	0
cat 2/86 – first injection	30·6±5·6	17·3±2·8	32·0±7·0	5·3±2·4
Kainic acid injection out of the p.h.–m.v.n. complex:				
cat 3/86 – first injection	29·0±3·0	21·0±3·5	27·0±6·1	20·0±4·2
cat 6/86 – first injection	26·0±4·9	20·0±5·8	23·0±6·2	22·0±3·7
cat 1/87 – third injection	—	—	—	—
Phosphate buffer injection in the p.h.:				
cat 1/87 – first injection	31·4±2·7	30·1±2·6	27·6±3·5	22·5±7·3
cat 1/87 – second injection	28·6±4·2	25·5±3·3	26·5±1·7	25·2±6·5

elicit any response either in the clockwise or in the anticlockwise direction (see Table 2).

The o.k.n. tested after the 60th minute was abolished in both directions (see Table 3).

In the other m.v.n. injections (cat 2/86, first injection excepted), we recorded a nystagmus whose linear slow phases were directed either to or opposite to the

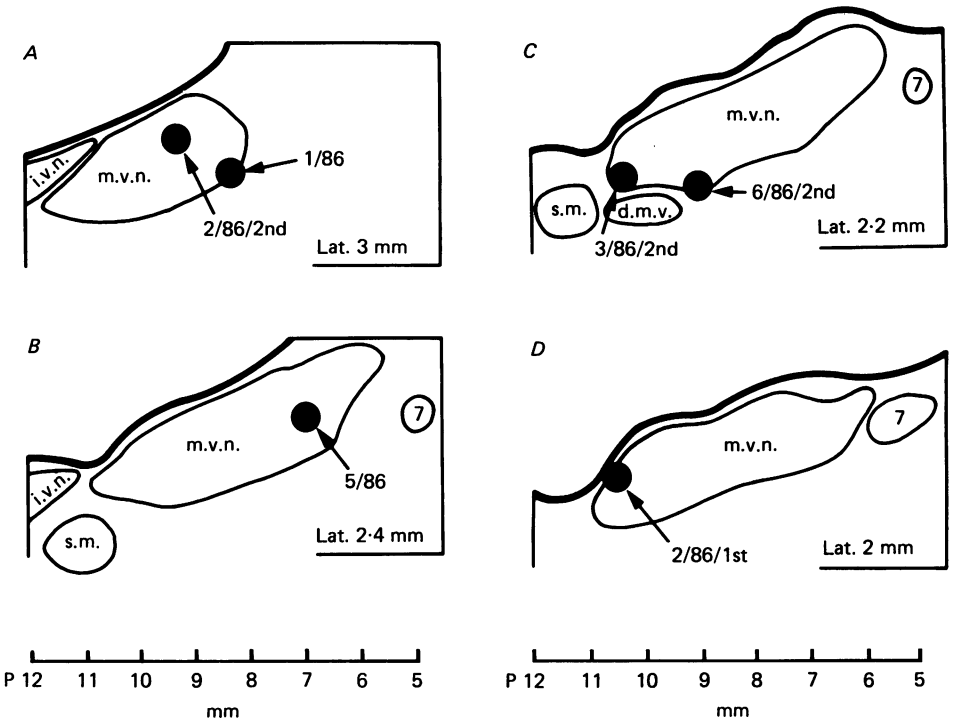

Fig. 7. Location of the six injections of kainic acid performed in the medial vestibular nucleus (m.v.n.). Parasagittal sections at lateral levels 3 mm (*A*), 2·4 mm (*B*), 2·2 mm (*C*) and 2 mm (*D*). I.v.n., inferior vestibular nucleus; d.m.v., dorsal motor nucleus of the vagus; s.m., medial nucleus of the solitary tract; 7, genu of the facial nerve. Large points indicate the injection sites. Identification system of the injections as in Fig. 2*A*.

injection site. It lasted between 1 and 30 min. The lapse of time after which a bilateral post-saccadic drift could be recorded varied from 6 to 31 min (see Table 1). The response to a velocity step of rotation was a step change in eye position never exceeding 4·3 deg in either direction. The o.k.n. was completely abolished in both directions (see Table 3).

The first injection in cat 2/86 was less disrupting than the preceding ones. A bilateral post-saccadic drift appeared only after 60 min and its minimal time constant was as long as 3·0 s (Table 1). The response to a step of rotation was a step change of eye position of 8 deg when the head rotated to the side of the injection and 2 deg when it rotated to the opposite direction. The o.k.n. was diminished but not abolished (Table 3).

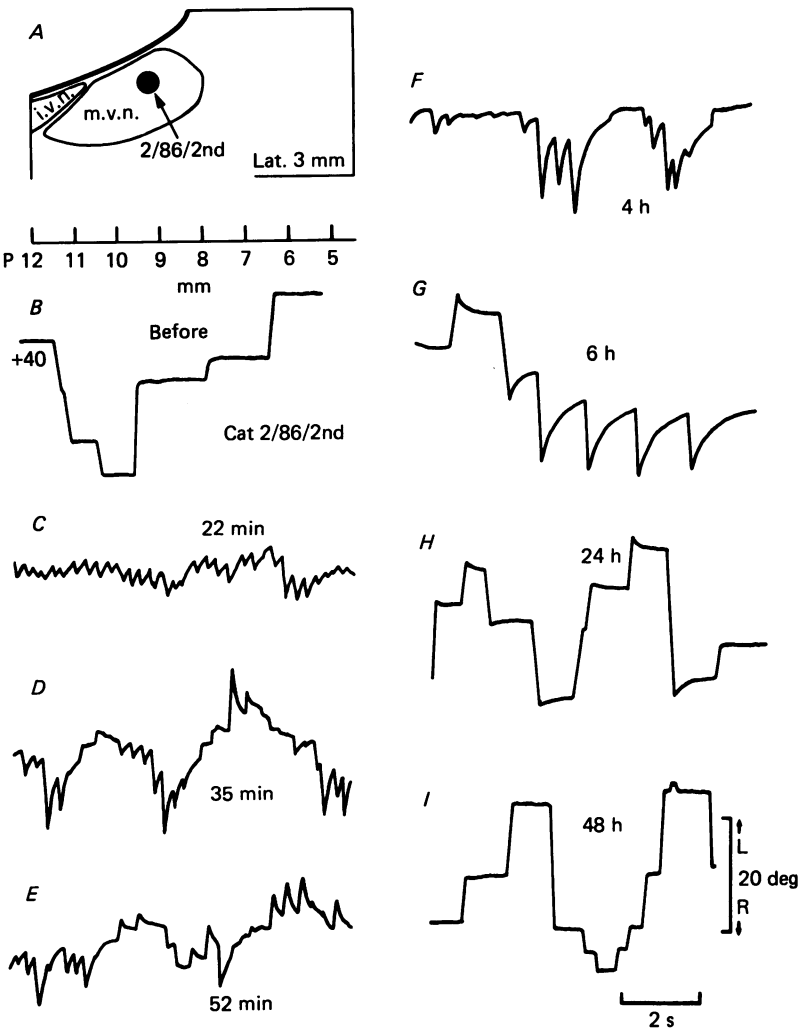

Fig. 8. Effect of kainic acid injection in the medial vestibular nucleus (m.v.n.) on saccades in light. *A*, location of the site of the injection (large point) whose effects are illustrated in *B–I*. I.v.n., inferior vestibular nucleus. Identification of the injection as in Fig. 2*A*.

Kainic acid injections out of the prepositus hypoglossi nucleus–medial vestibular nucleus

Three injections were performed out of the p.h.–m.v.n. complex, two in the medial longitudinal fasciculus (m.l.f.) (see insert in Fig. 9) and one in the magnocellular tegmental field of the reticular formation (Fig. 10*A*).

After kainic acid injection in the m.l.f., eye movements were less disrupted than after injection in the p.h.–m.v.n. complex. The time constant of the exponential post-saccadic drift never dropped below 0·8 s (Table 1 and Fig. 9). Its latency for occurring was 15 min in one case and 18 min in the other and the delay for complete recovery was very short: 1 h in each case (Fig. 9). The gain of the sinusoidal v.o.r.

was reduced but no phase advance was detected (Table 2). Furthermore the maximal velocity of the o.k.n. decreased only slightly (Table 3).

The pattern of the pathological movements induced by the third injection in cat 1/87 was completely different from those observed in previous injections. Notice that the third injection was performed after two injections of phosphate buffer devoid of effect. It is interesting to point out that the injection site was 4 mm away from the p.h.–m.v.n. complex, so that effects due to diffusion towards these nuclei are unlikely (Fig. 10*A*).

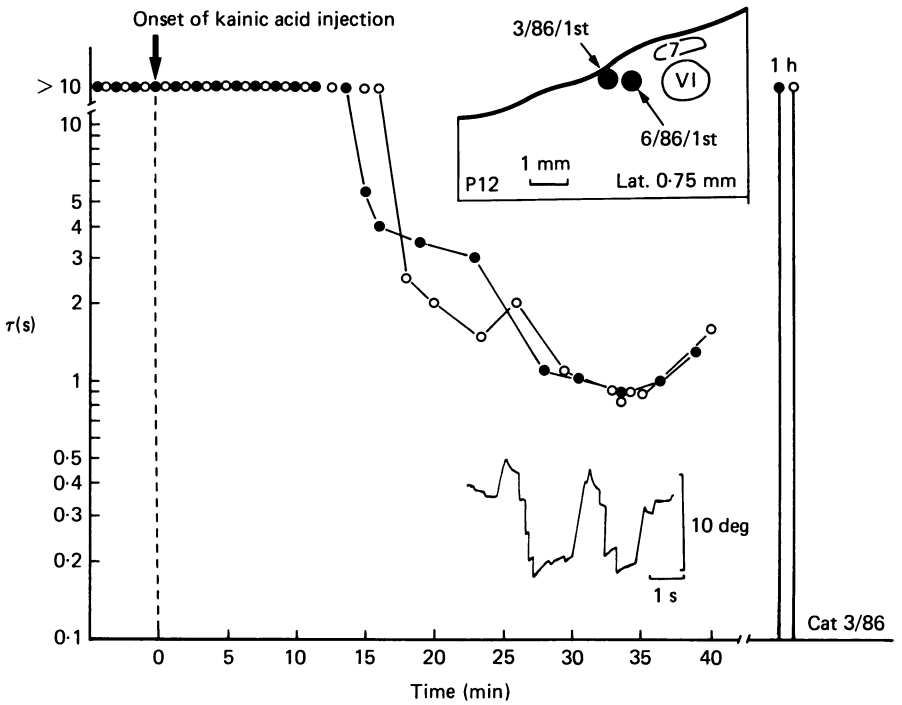

Fig. 9. Time constant of the post-saccadic drift of spontaneous saccades (ordinate) in the light as a function of time (abscissa) after the start of unilateral kainic acid injection in the right medial longitudinal fasciculus of cat 3/86 (first injection). ●, left-directed saccades. ○, right-directed saccades. Notice the mild post-saccadic drift. Time constant does not drop below 1 s. Notice also the rapid recovery (1 h). Upper insert, location of the injections sites in the m.l.f. indicated by large points. Identification system of the injections as in Fig. 2*A*. Lower insert, spontaneous saccades occurring 30 min after the start of kainic acid injection.

The injection produced a progressive reduction of the frequency and of the amplitude of the saccades in both directions (Fig. 10*B–D*). After about 37 min no further saccades were observed. The major result pointed out by this experiment was the lack of any post-saccadic drift. The primary position of gaze was deviated to the side of the injection by about 20 deg (Fig. 10*Ea* and *b*). The v.o.r. in response to a sinusoidal head rotation in darkness was asymetrical. During rotation of the head to the right, the movement of the eyes was stopped in the right corner of both eyes. The

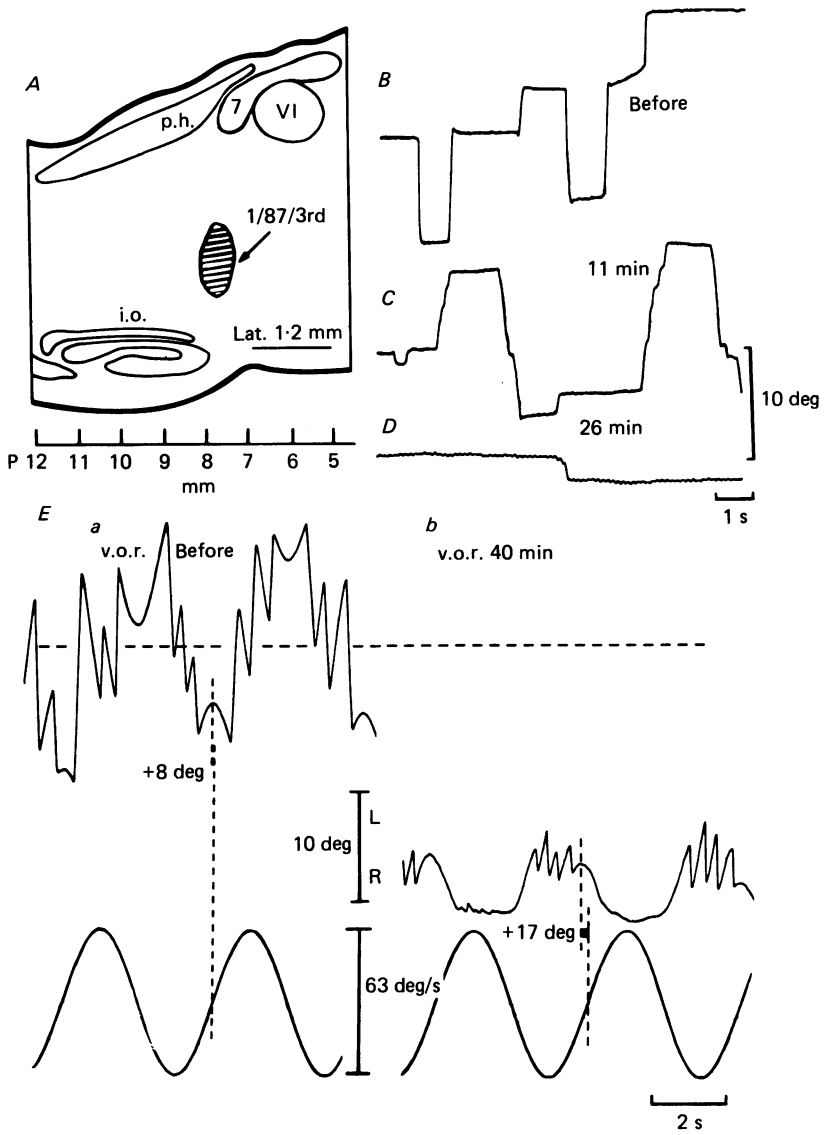

Fig. 10. Effects of injections of kainic acid in the magnocellular tegmental field of the reticular formation on the saccades in light and on the vestibulo-ocular reflex in the dark. *A*, location of the injection. Same abbreviations as in Fig. 2*A*. The extension of the lesion site is marked by a hatched area. *B–D*, spontaneous saccades before (*B*), 11 min after (*C*) and 26 min after (*D*) kainic acid injection. Notice the reduction of both the frequency and the amplitude of the saccades. *E*, v.o.r. tested in darkness at 0·10 Hz before (*a*) and after (*b*) kainic acid injection. After the latter the neutral point of the gaze is deviated to the side of the injection (compare *a* and *b*). Notice that the response is asymmetrical.

phase advance grew up from +8 deg before (Fig. 10*Ea*) to only +17 deg after (Fig. 10*Eb*) the injection. The mechanical jamming of the eye in the right corner prevented us from validly assessing the gain of the v.o.r. The o.k.n. was not tested in this cat.

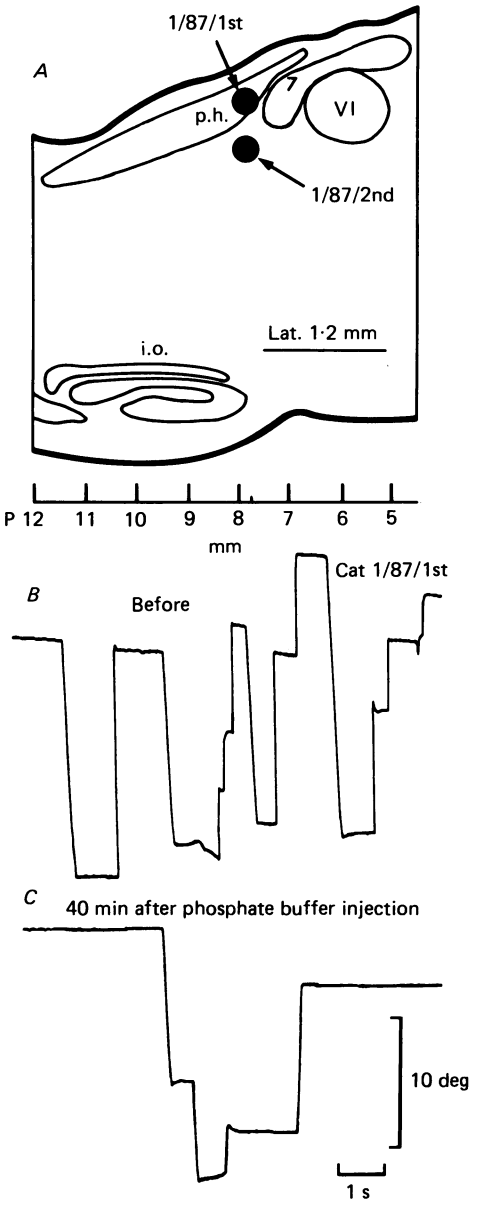

Fig. 11. Effect of phosphate buffer injection either in the p.h. or 1 mm deeper on the saccades in light. *A*, location of the injection sites indicated by large points. Same abbreviations and same identification system for the injections as in Fig. 2*A*. *B*, saccades before the injection. *C*, saccades 40 min after the start of the injection. Notice the lack of any post-saccadic drift.

Phosphate buffer injection

To test the selectivity of the effect of kainic acid, phosphate buffer without any kainic acid was injected in the p.h.–m.v.n. complex of cat 1/87. Two injections were performed at a 2 h interval, the first in the p.h. and the second at 1 mm deeper than

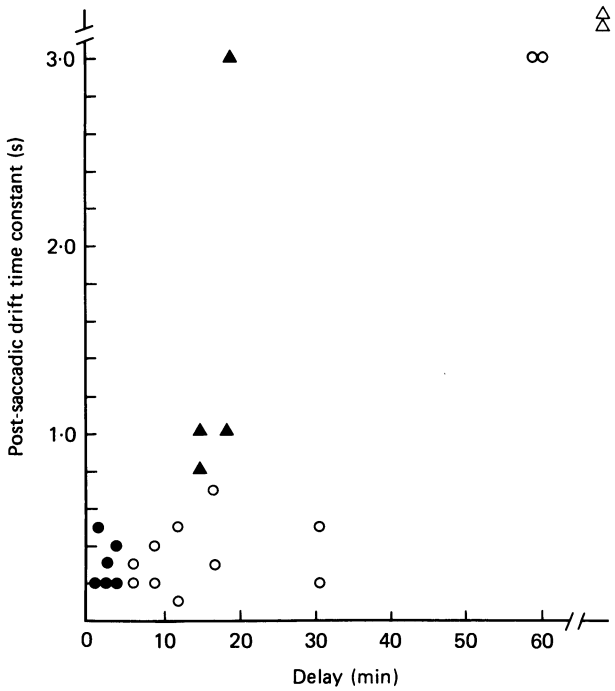

Fig. 12. Diagram summarizing the characteristics of the post-saccadic drifts induced by our various injections of kainic acid. Two points correspond to each injection: one is related to the left-directed saccades and the other to the right-directed saccades. The minimal value achieved by the time constant of the exponential post-saccadic drift (ordinate) is plotted against the delay for a post-saccadic drift to become detectable (abscissa). ●, injections in the p.h.; ○, injections in the m.v.n.; ▲, injections in the m.l.f.; △, injections in the magnocellular tegmental field of the reticular formation. Notice that points related to each of these five locations tend to be arranged in groups with a notable exception: the values recorded during the first injection in cat 2/86 are not in the same range as those of the other injections in the m.v.n. (see the two circles in the upper-right corner). The two open triangles in the upper-right corner where both co-ordinate axes are interrupted represent lack of post-saccadic drift following kainic acid injection in the magnocellular tegmental field of the reticular formation.

the first (Fig. 11*A*). We observed neither a post-saccadic drift (Fig. 11*B* and *C*), nor a significant modification of the v.o.r. (Table 2).

DISCUSSION

Where is the neural integrator?

Of course, one would expect a complete failure of the neural integrator if kainic acid is injected into its centre. But what would happen if kainic acid is injected 0·5 or 1 mm away from it? Diffusion of kainic acid will occur; kainic acid will reach the neural integrator and disrupt it, but the concentration of kainic acid is the greatest at the site of injection and decreases with the distance away from it. As a result, the nearer the injection site is to the centre of the integrator, the more powerful and the more rapid is the defect.

Figure 12 brings together the data about post-saccadic drifts (in the light) induced by our kainic acid injections in various locations of the medulla. In this Figure, the magnitude of the defect of the gaze-holding system, assessed by the minimal time constant of the post-saccadic drift, is plotted against the delay after which a post-saccadic drift is detectable. Two points correspond to each injection, one for the left-directed saccades and the other for the right-directed saccades.

From these above remarks, it would be expected that the nearer the injection is to the integrator, the nearer the associated points are to the lower left corner of the graph. Inspection of Fig. 12 shows that the nearest points from that corner correspond to injections in the p.h. (●), followed by those related to injections in the m.v.n. (○), followed in turn by those associated with injections in the m.l.f. (▲) and in the magnocellular tegmental field of the reticular formation (△). Such an analysis suggests that the p.h.–m.v.n. complex is the location of the neural integrator.

But as our p.h. injections were made near the edge of the ventricle, it is important to wonder whether the observed defects were not due to leakage of kainic acid into the ventricle and from there to other cerebral regions. The fact that the two circles in the upper right corner of Fig. 12 correspond to the injection performed at the edge of the ventricle (see Fig. 7*D*) is evidence against such an indirect effect of our p.h. injections.

The m.l.f. is a bundle of axons. The action of kainic acid is known to depend on its binding to receptors located on neurones but lacking on axonal fibres (Coyle *et al.* 1978; McGeer *et al.* 1978). Injection in the m.l.f. produced a mild defect of the neural integrator probably because of diffusion of kainic acid from the m.l.f. to the neighbouring p.h. nucleus. Injections in the magnocellular tegmental field of the reticular formation produced no deficit at all of the neural integrator. These negative results (mild effect in the m.l.f. and lack of effects in the magnocellular tegmental field of the reticular formation) observed with injections out of the p.h.–m.v.n. complex strengthen the hypothesis that integration processing takes place in the p.h.–m.v.n. complex. We conclude that the neural integrator is located within the p.h.–m.v.n. complex.

We will now discuss the respective roles of the p.h. and the m.v.n. There are four possibilities: (1) the neural integrator could be in the p.h. and its output sent directly to the oculomotoneurones; (2) the neural integrator could be in the m.v.n. whose output would be sent to the oculomotoneurones; (3) the integration processing could be done by both the p.h. and the m.v.n. nuclei; (4) the neural integrator could be in the p.h. and its output would be sent to the oculomotoneurones *via* the m.v.n.

The first possibility is ruled out by the fact that the pathway linking the m.v.n. and the oculomotoneurones carries not only a velocity signal but also a position signal (Pola & Robinson, 1978). This means that the output of the neural integrator reaches the oculomotoneurones after being relayed in the m.v.n. The second possibility excludes the p.h. from the integration processing. However, the failure of the neural integrator induced by injection in the p.h. cannot be related to some diffusion of kainic acid towards the m.v.n., as the deficit induced by kainic acid appears sooner when injected in the p.h. than when injected in the m.v.n. (see Fig. 12). There is no evidence from our results to rule out either the third or the fourth possibilities; our results agree with both of them.

Unilateral injection versus bilateral effects

At first sight it is surprising that a unilateral injection of kainic acid induced a bilateral gaze-holding defect. A possible interpretation would be that kainic acid injected in one side would diffuse to the contralateral side. Diffusion certainly explains a few of the pathological effects induced by kainic acid. For instance, in both the p.h. and the m.v.n. injections, there is a loss, after a delay, of both ipsi- and contralateral saccades. This means that if the injected kainic acid damages first the integrator, it later invades the horizontal pulse generators for saccades. However, the gaze-holding defect of the contralateral saccades cannot be due to diffusion, as the post-saccadic drifts occurred simultaneously (and not one after the other) in both directions. Another interpretation is based on the richness of the commissural connections. When talking about neural integration processing, neurophysiologists say: 'the' neural integrator. Even if a single plane of rotation is concerned, it is an over-simplification. In the horizontal plane, the neural integrator holds the position of the eyes for both the left and the right. Integration may be done by a pair of integrators, connected reciprocally and working in 'push–pull' (Zee, Yamazaki, Butler & Gücer, 1981). Other models even proposed that the integration is the result of connections between the two sides (Cannon, Robinson & Shamma, 1983; Galiana & Outerbridge, 1984). Recent neuroanatomical studies also emphasized the abundance of commissural connections between the left and the right m.v.n.–p.h. complexes: the two m.v.n.s (left and right) are interconnected (Shimazu & Precht, 1966) and the two p.h.s too (McCrea & Baker, 1985). Each p.h. projects onto the ipsi- and contralateral m.v.n.; each m.v.n. projects onto the ipsi- and contralateral m.v.n. (McCrea & Baker, 1985). In such a case, it would not be surprising that the introduction of a perturbation in one side of the integrator machinery would disturb the whole processing.

Histopathological effects of kainic acid

When injected in the magnocellular tegmental field of the reticular formation following our procedure of delivery (see Methods), 2 μg of kainic acid induced a virtually complete loss of neuronal cell bodies. By contrast, the same injection in the p.h. or in the m.v.n. did not induce any permanent structural damage. This probably reflects a reduced number of kainic acid binding sites in these regions. A similar problem was encountered by Henn *et al.* (1984), who had to use unusually high concentrations of kainic acid (4–8 μg/μl) to produce lesions in the p.p.r.f. It seems that in our experiments kainic acid did not kill the neurones but made them 'sick'. In this respect it is interesting to point out that two injections of kainic acid at the same site (cat 5/85) performed at a 1 week interval caused pathological eye movements appearing after the same latency. Let us assume that the first injection of kainic acid killed neurones and that recovery was due to the surviving neighbouring neurones. In this case the second injection among dead neurones would not induce a failure of the neural integration processing by acting on those neurones but by diffusion of kainic acid to the near neurones in good health. As this process takes time, pathological eye movements would appear at a longer latency after the second injection than after the first. However, we found this not to be the case.

Comparison with our previous electrolytic lesions study

In a previous paper (Cheron *et al.* 1986), we made electrolytic lesions in the region of the p.h. nucleus. We observed disabling of the neural integrator only in cases where the whole of the p.h., its rostral pole included, was destroyed. We failed to record any sign of neural integrator failure if the posterior four-fifths of the p.h. were destroyed, sparing the rostral pole. This is in contrast with the present observation where severe neural integrator failure was seen after kainic acid injection in the middle or in the caudal pole of the p.h.

We would like to compare this paradox with that observed by Hikosaka & Wurtz (1985) working on the superior colliculus. This is well known to be involved in the initiation of saccades (Wurtz & Albano, 1980). Whereas ablation of the superior colliculus produce mild deficits in saccades (Wurtz & Goldberg, 1972; Schiller, True & Conway, 1980; Albano & Wurtz, 1982), microinjections of muscimol into it cause severe deficits in eye movements (Hikosaka & Wurtz, 1985). Hikosaka & Wurtz (1985) interpret this paradox as the ability of the brain to compensate over time for partial dysfunction.

Similarly, in our previous electrolytic lesions, animals were tested post-operatively on the 4th day. Such a lapse of time after the lesion would be enough for other brain areas to compensate for some deficits induced by partial lesions in the neural integrator underlying structure. The ability of the brain to *rapidly* compensate and the present results with kainic acid lead us to reinterpret our previous results concerning electrolytic lesions in the p.h. nucleus (Cheron *et al.* 1986). Effects of kainic acid injection showed that the caudal half of the p.h. was involved in the integration processing; the lack of any defect of the neural integrator after electrolytic lesion in the posterior four-fifths of the p.h. was probably due to compensation from other areas. Signs of neural integrator failure were observed only after extensive electrolytic lesions in the region of the p.h. nucleus, that is when destruction of enough areas involved in the neural integration processing prevented compensation.

This new interpretation fits well with the fact that neurones of the p.h., whose encoded variables are either the position or the eye position and velocity, are encountered throughout the rostrocaudal extension of the nucleus (Lopez-Barneo *et al.* 1980).

Conclusion

This study provides support for the hypothesis that the medial vestibular–prepositus nuclear complex is the underlying structure of the neural integrator.

APPENDIX

The optokinetic system has the general structure of a negative feed-back loop (Fig. 1*C*). The forward pathway includes a differentiator (s), a velocity-storage element (v.s.e.), a network with a direct pathway and an integrator (n.i.) in parallel and the plant. The v.s.e. is formed by a leaky integrator and a positive feed-back loop whose gain is k. In a former paper (Cheron *et al.* 1986), we computed the transfer function

of the whole optokinetic processing. In Laplace transform notation, it is in open loop:

$$H(s) = \frac{n}{snT+1}, \tag{1}$$

and in closed loop:

$$R(s) = \frac{H(s)}{1+H(s)}, \tag{2}$$

where $n = 1/(1-k)$ and T is the time constant of the leaky integrator of the v.s.e. The parameters T and k were determined to be 2·6 s and 0·65 respectively in the cat.

In this former computation we omitted gain factors as we focused our attention on the time constants of the response. In this paper we need to predict the optokinetic response to a rotation of the drum at a constant velocity of 30 deg/s in the normal cat and after complete disabling of the neural integrator. A gain factor must be introduced. All scale factors can be replaced by one equivalent net gain, g_{ok}. Hence

$$H(s) = g_{ok}\frac{n}{snT+1}. \tag{3}$$

The gain of the open-loop optokinetic system (g_{ok}) is known to be dependent on the velocity of the optokinetic stimulus. It is available from a recent study (Magnin, Salinger & Kennedy, 1986), using cats with a paralysed eye. When the surrounding moved at a velocity of 30 deg/s from the temporal side to the nasal side of the paralysed eye, the gain of the optokinetic system (computed from the movement of the covered eye) was 1·5. When the same stimulus moved in the opposite direction, the gain was 0·5. In a normal cat, the surrounding movement stimulates both eyes, one in the temporo-nasal direction, the other in the naso-temporal direction. Hence, for a stimulus velocity of 30 deg/s, the gain of the optokinetic system in open loop (g_{ok}) can be assumed to be 2 (1·5+0·5).

Computation with such a gain predicts that, in the normal cat, the velocity of the eye would reach a ceiling at 25·5 deg/s after 10·5 s. In case of total failure of the neural integrator, the eye velocity would reach a maximum of only 3 deg/s at 0·6 s and decrease afterwards to be as small as 0·3 deg/s after 20 s.

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