

Loss of the Neural Integrator of the Oculomotor System from Brain Stem Lesions in Monkey

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SUMMARY AND CONCLUSIONS

1. Eye movements were recorded from four juvenile rhesus monkeys (*Macaca mulatta*) before and after the injection of neurotoxins (kainate or ibotenate) in the region of the medial vestibular and prepositus hypoglossi nuclei, an area hypothesized to be the locus of the neural integrator for horizontal eye movement commands. Eye movements were measured in the head-restrained animal by the magnetic field/eye-coil method. The monkeys were trained to follow visual targets. A chamber implanted over a trephine hole in the skull permitted recordings to be made in the brain stem with metal microelectrodes. The abducens nuclei were located and used as a reference point for subsequent neurotoxin injections through cannulas. The effects of these lesions on fixation, vestibuloocular and optokinetic responses, and smooth pursuit were compared with predicted oculomotor anomalies caused by a loss of the neural integrator.

2. Kainate and ibotenate did not create permanent lesions in this region of the brain stem. All the eye movements returned toward normal over the course of a few days to 2 wk. Histological examination revealed that the cannula tips were mainly located between the vestibular and prepositus hypoglossi nuclei, in their rostral 2 mm, bordered rostrally by the abducens nuclei. Dense gliosis clearly demarcated the cannula tracks, but for most injections there were no surrounding regions of neuronal loss. Thus the eye movement disorders were due to a reversible, not a permanent, lesion.

3. The time constant for the neural integrator was determined from the velocity of the centripetal drift of the eyes just after an ec-

centric saccade in total darkness. For intact animals this time constant was >20 s. Shortly after bilateral injections of neurotoxin, the time constant began to decrease and reached a minimum of 200 ms; every horizontal saccade was followed by a rapid centripetal drift with a time constant of ~200 ms. For vertical eye movements, in this acute phase, the time constant was ~2.5 s.

4. The vestibuloocular reflex (VOR) was drastically changed by the lesions. A step of constant head velocity in total darkness evoked a step change in eye position rather than in velocity. In the absence of the neural integrator, the step velocity command from the canal afferents was not integrated to produce a ramp of eye position (normal slow phases); rather this signal was relayed directly to the motoneurons and caused a step in eye position. The per- and postrotatory decay of the head velocity signal was decreased to 5–6 s indicating that vestibular velocity storage was also impaired. Loss of velocity storage, however, could be dissociated from integrator failure.

5. Optokinetic stimulation with a step in drum velocity also caused a step change in eye position. Just as with the VOR there was no integrator to generate a ramp eye-position signal from the step eye-velocity command. Optokinetic velocity storage was also damaged in a manner similar to that seen in the VOR.

6. Smooth pursuit was impaired by the neurotoxin injections. Within the first few hours after injection, the animals were unable to track small visual targets. With the assumption that the initial response to full-field stimulation with an optokinetic drum is due to pursuit, it was found again that a step of drum velocity produced a step in eye position.

7. These abnormalities developed simul-

taneously for each class of eye movement after every lesion and support the hypothesis that a final common integrator is used by all conjugate subsystems of the oculomotor system and that the integrator for horizontal eye movements is located in the region of the medial vestibular and prepositus hypoglossi nuclei.

INTRODUCTION

All primate conjugate eye movements are initially encoded by premotor brain stem neurons as eye-velocity signals; the modulation in discharge rate is proportional to desired eye velocity. Such signals are seen on second-order vestibular neurons for vestibular and optokinetic movements (41), on burst neurons for saccades (17), and on gaze-velocity Purkinje cells for pursuit (28). The firing rates of the motoneurons of the extraocular muscles, however, modulate with both eye position and eye velocity. The eye-position signal is created from the velocity command by integration, with respect to time in the mathematical sense, and sent to the motoneurons in combination with the eye-velocity command. The population of neurons that performs this process has been named the neural integrator. Robinson (32) has reviewed experimental evidence and presented theoretical arguments in support of the hypothesis that a single, final, common integrator network is used by all the conjugate eye movement systems (saccadic, vestibuloocular, optokinetic, and smooth pursuit) as shown in Fig. 1. Although the evidence in

favor of a single final common integrator is substantial, until now, definitive proof has been lacking, and there is one report that proposes separate integrators for the saccadic and vestibuloocular systems (18).

The necessity for a neural integrator in the premotor processing of the oculomotor system has been appreciated for almost 20 yr (30). However, the anatomical locus of the integrator has remained elusive. Four anatomical sites have been proposed. In historical order they are the paramedian pontine reticular formation (PPRF), cerebellum, vestibular nucleus (VN), and the nucleus prepositus hypoglossi (NPH).

Daroff and Hoyt (12) briefly reviewed clinical cases and experimental lesions in which the PPRF was involved. In most cases a unilateral lesion led to a loss of all ipsilateral conjugate eye movements. These authors proposed that a crucial link in the premotor pathway had been destroyed; perhaps it was the final common integrator. When Cohen and Komatsuzaki (9) applied a train of constant-frequency electrical pulses to the monkey PPRF, the eyes deviated ipsilaterally at a constant velocity. At the end of the stimulus the eyes remained in the new position for several hundred milliseconds, the duration of a natural fixation. Since the eye deviation was proportional to the integral of the stimulus waveform, these authors concluded that the integrator was in the PPRF. This result, however, only means that the PPRF projects to the integrator, not that it contains it. Finally Keller (22) described units, but only a few, in the

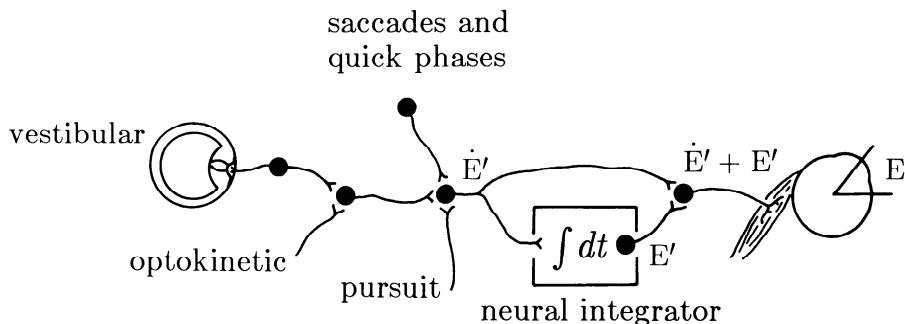


FIG. 1. The final common integrator hypothesis. All eye movement commands are initiated as eye-velocity encoded signals, E' , which then enter the neural integrator to provide the eye-position encoded signal, E' , present on the motoneuron. The arrangement is schematic and is only intended to show that all eye-velocity signals are passed directly to the motoneurons along with the integrated eye-position signals and is not intended to represent neurons actually involved in this process.

PPRF that carried a pure position signal and hence were assumed to be direct outputs of the neural integrator. The PPRF hypothesis was only recently disproved by Henn and colleagues (20) who made selective lesions in the monkey PPRF with the neurotoxin kainate. Unilateral lesions abolished all ipsilateral saccades and quick phases of nystagmus, but ipsilateral slow eye movements, and particularly the ability to maintain eccentric gaze, were preserved, which means that the neural integrator remained intact.

Carpenter (6) showed that either cerebellectomy or cooling the cerebellum in the decerebrate cat caused a low-frequency phase advance and gain decrease in the VOR indicating that the integrator had been effectively destroyed (the integrator time constant was reduced to 0.1 s). In the chronic cerebellectomized cat (no decerebration), however, Robinson (31) found that the integrator time constant was only reduced to 1.3 s. He suggested that there is a rather leaky brain stem integrator and that somehow the cerebellum improves its performance so that it normally has a time constant of ~20 s. Westheimer and Blair (42) also reported that gaze-evoked nystagmus was prominent in cerebellectomized adult monkeys; after every eccentric saccade the eyes drift centripetally, the sign of a leaky integrator. Zee et al. (45) demonstrated that surgical ablation of only the flocculus and paraflocculus in monkey caused a similar degree of integrator deficit.

In the mid 1970s single-unit recordings were first obtained from the VN in the alert monkey (23, 27). A surprising result was that many vestibular neurons, even second-order neurons, carried an eye-position signal, regardless of whether the eye movement was of vestibular origin or not. This led these investigators to note parenthetically that perhaps the VN forms part of the neural integrator. Tomlinson and Robinson (38) studied oculomotor signals in the superior vestibular nucleus of the monkey and discovered unitary responses with virtually every possible combination of head-velocity, pursuit-velocity, saccadic burst or pause, and eye-position signals. They hypothesized that the integrator may reside in the VN, and that these signals represent spatial mixing of signals projecting from different oculomotor systems to a single integrator. In addition Galiana and Outer-

bridge (16) have presented a theoretical model in which integration may be performed by positive feedback through commissural vestibular connections.

Anatomical (19, 26), electrophysiological (1), and neurophysiological (2, 25) investigations have shown that the NPH is extensively interconnected with the oculomotor and vestibular systems. It receives afferents from and projects to virtually all the oculomotor centers of the brain stem and cerebellum (major afferents from contralateral NPH, VN, reticular formation, flocculus; major efferents to flocculus, VN, inferior olive, reticular formation, superior colliculus, and extraocular motor nuclei), and many of these neurons modulate their firing rates in relation to eye position and velocity (25) prompting the suggestion that the neural integrator may be located in the NPH. Finally, Cheron and colleagues (7, 8) discovered, independently from and simultaneously with the present study, that electrolytic lesions of the NPH in cat, particularly of the rostral pole, cause permanent derangements of vestibular, saccadic, and optokinetic eye movements consistent with a complete loss of the neural integrator; that is, more complete than in chronic cerebellectomized animals.

The goal of this study was to provide more definitive evidence for the anatomical location of the neural integrator. Based on the evidence reviewed above, we set out to test the hypothesis that the neural integrator was located in the region of the NPH and VN [particularly, for horizontal movements, the medial vestibular nucleus (MVN)]. Since it is difficult for any recording strategy to prove unequivocally that an isolated neuron was participating in the process of integration, the approach of this study was to make small injections of neurotoxins (kainate or ibotenate) in the chronic monkey preparation in the region of the MVN and NPH and then to observe their effects on eye movements in light of explicitly predicted anomalies that would be caused by a loss of the neural integrator.

METHODS

General experimental procedures

Four rhesus monkeys, *Macaca mulatta*, were prepared for chronically measuring eye movements and recording from single units. All surgery was performed under aseptic conditions using pento-

barbital anesthesia and prophylactic antibiotic coverage. Eye movements were recorded monocularly in the head-restrained animal with the magnetic field/search-coil technique (15). In the first operation a coil of teflon-coated wire was implanted between the conjunctiva and sclera using the method of Judge et al. (21). Its lead wires were passed subcutaneously to a connector at the top of the head. Next a pedestal was secured to the skull with dental cement and stainless steel screws to allow immobilization of the head during recording sessions. Eye movement recording and training sessions began 1 wk later. The noise level of the eye-movement recording system at the sensitivity used was 15 min of arc, and the system was calibrated by having the trained animal fixate illuminated targets at $\pm 20^\circ$ horizontally and vertically. Eye movements were recorded simultaneously on FM tape and an ultraviolet, mirror-galvanometer recorder (overall bandwidth 0–1 kHz). Eye velocity signals were also recorded from analog differentiators for rapid (-3 dB cut off at 48.8 Hz) and slow (10.3 Hz) eye movements. All data were analyzed by hand from the recorded tracings.

In a second operation performed 1 mo later a stainless steel recording chamber was mounted over a trephine hole in the occiput, stereotactically aligned on the midline with the axis tilted 25° back from the vertical in the sagittal plane. The center of the chamber was directed toward the midpoint between the abducens nuclei according to the atlas of Smith et al. (36) (lateral 0 mm, posterior 3.0 mm, up 2.0 mm). This placement enabled recordings to be made from the level of the trochlear nucleus through the rostral medulla, including the vestibular nuclei.

Behavioral testing

Each animal was trained under a water reinforcement paradigm to fixate or pursue a spot of light backprojected on an $80 \times 80^\circ$ tangent screen via a mirror galvanometer. The horizontal VOR was measured by imposing steps of constant-velocity chair rotation (between 30 and $90^\circ/\text{s}$) in total darkness. Optokinetic responses were elicited by enclosing the monkey in a rotating drum covered with large, variously sized black circles on a white background. Constant velocity rotations were used and a light within the drum was turned on and off during rotations. In these tests alertness was maintained by auditory stimuli and intermittent water reinforcement. Smooth pursuit was tested by requiring the animal to track the target moving in a triangular waveform in a dimly lit room. The amplitude was $\pm 10^\circ$ or $\pm 20^\circ$, horizontally or vertically, at frequencies of 0.2 or 0.4 Hz. Saccades were recorded during spontaneous eye movements in the dark and for target-directed movements between 0 and ± 10 or $\pm 20^\circ$ horizontally or vertically.

Unit recording and stimulation

Monopolar tungsten electrodes were used to record single units and to stimulate. Electrodes were insulated with an exposed tip that was ferroplated to achieve an impedance of 0.5 – 3.0 M Ω at 1 kHz. Electrodes were advanced into the brain stem with a hydraulic microdrive. The electrode was inserted initially within a guide tube (21-gauge needle) to puncture the dura and tentorium. Once in place, the tip of the guide tube was 4–6 mm above the floor of the fourth ventricle.

The abducens nuclei were clearly discernible from the characteristic "singing" quality of the motoneuron firing rates heard on an audio monitor that correlated closely with horizontal eye movements, and by their size and sharp boundaries. The abducens nuclei were then used as a landmark from which a map of the brain stem could be constructed relative to the chamber. Stimulation was used to map the eye movements evoked from the region of the NPH and VN, and also to help in judging the error in electrode placement when the initial penetrations failed to encounter an abducens nucleus. Brief trains of monopolar electrical stimulation at $20\text{-}\mu\text{A}$ intensity (0.5-ms pulses at 200 Hz, cathodal) were delivered from a stimulus isolation unit for 0.5–2.0 s, and the evoked eye, limb, and facial movements were observed.

Lesion studies

Neurotoxins were injected via a 29-gauge cannula that was advanced through the electrode guide tube to locations previously determined by recording and stimulation. The cannula was connected to a Hamilton microsyringe and 1- to $3\text{-}\mu\text{l}$ injections were made over 6 min by advancing the syringe plunger with a stepper motor. Ibotenate (Sigma, Regis) was dissolved in phosphate buffer to a concentration of $10\text{ }\mu\text{g}/\text{\mu}\text{l}$ and injected in one monkey. For the other three monkeys, kainate (Sigma) at a concentration of 2 – $4\text{ }\mu\text{g}/\text{\mu}\text{l}$ was injected. At the end of all experiments the monkeys were perfused under deep pentobarbital anesthesia with an intra-aortic injection of 10% neutral formalin. The brains were blocked and fixed in celloidin for two animals and cut from frozen sections in the other two. Each slice was 20 or $40\text{ }\mu\text{m}$ thick (celloidin vs. frozen), and alternate sections were stained for Nissl substance or myelin.

RESULTS

Electrophysiological identification of injection sites

The following criteria were used to identify the abducens nuclei on the basis of single-unit recordings: 1) cells should have position-burst (also called burst-tonic) activity for ipsilateral

horizontal eye movements and no modulation for vertical eye movements; 2) the modulation in firing rate should be tightly coupled to eye position during fixation so that the audio monitor of unit activity indicates a very machinelike, frequency-modulated encoding of eye position; 3) the cell packing density should be very high; 4) every cell should have similar behavior with no extraneous response properties; 5) a penetration through the center of one nucleus should reveal a 2-mm continuous region of cells with the above properties; 6) as the electrode is repositioned successively further left, right, anterior, or posterior from the center, the above activity should be lost abruptly after ~ 1.0 mm. In all four monkeys, the abducens nucleus was not encountered when penetrations were made based on stereotaxic estimates but were found 2–4 mm caudal to the expected coordinates.

Recording tracks were then made from 0.5 to 3.5 mm caudal to the abducens nuclei, over the range from midline to 4 mm lateral. The responses of units in this region were compared qualitatively with the reported activities of NPH neurons in the cat (25) and the unitary responses of the MVN (23, 27). The goal was

simply to identify a region compatible with reported properties of cells in these nuclei. Encountered were position-burst activity for ipsilateral eye movements and vestibular-only activity of both type I and type II. Units with modulation related to eye position and velocity differed from abducens motoneurons in that they were scattered instead of tightly clustered, and the modulation seemed more loosely coupled to eye movements. These responses were judged compatible with the reported unit behavior in the NPH and MVN. Since isolated units were widely scattered, stimulation was used as an aid in the final selection of injection sites because it was felt to produce a more global representation of areas in the brain stem related to eye movement.

Stimulating caudal to the abducens nuclei produced nystagmus as shown in Fig. 2A. In general the slow phases were horizontal and ipsilateral. Stimulation of the vestibular nerve, of course, evokes contralateral slow phases (10). Other studies (37) of stimulation in the VN have also shown contralateral slow phases, but anesthetized monkeys and current intensities greatly in excess of $20\ \mu\text{A}$ were used (see DISCUSSION). We found that stimulation of

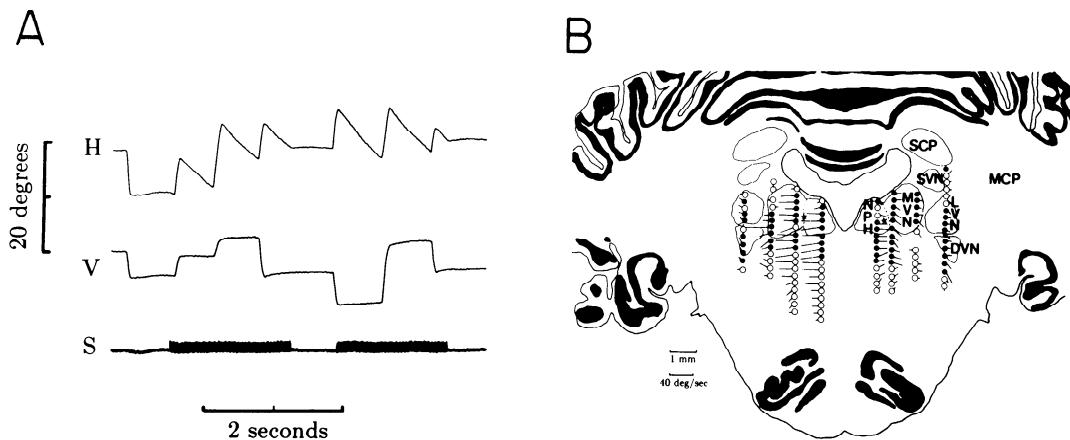


FIG. 2. Eye movements and a slow-phase velocity map of stimulation-induced nystagmus. *A*: nystagmus evoked from stimulating the left medial vestibular nucleus. H and V denote horizontal and vertical eye movements, upward deflection for right and up, and S is the stimulation. *B*: map of the slow-phase velocity during evoked nystagmus. Each circle shows the site of electrical stimulation at $20\ \mu\text{A}$ on a transverse section of the brain stem, 1 mm caudal to the level of the abducens nuclei, in the plane of the electrode tracks. Closed circles indicate nystagmus, open circles denote linear or exponential eye movements without quick phases. Each line segment is a vector representation of the direction and magnitude of the initial velocity of the induced eye movement. The two asterisks indicate a pair of injection sites chosen from these data. Abbreviations: DVN, descending vestibular nucleus; LVN, lateral vestibular nucleus; MCP, middle cerebellar peduncle; MVN, medial vestibular nucleus; NPH, nucleus prepositus hypoglossi; SCP, superior cerebellar peduncle; SVN, superior vestibular nucleus.

the NPH and MVN almost always produced ipsilateral slow phases. A typical map of these slow-phase velocities is shown in Fig. 2B. Each line segment is the (vector) sum of the horizontal and vertical components with its origin at the stimulus location. The transverse section through the brain stem is in the plane of the electrode tracks, tilted backward 25° from stereotaxic vertical, and located 1.0 mm caudal to the abducens nuclei. In all four monkeys nystagmus was elicited from sites immediately caudal to the abducens nuclei and extending to 3.0–3.5 mm lateral to the midline. The magnitude of the slow-phase velocity elicited by the constant 20- μ A stimulation decreased smoothly as penetrations were made lateral to 2.0 mm from the midline and as the electrode was moved from 1.0 to 4.0 mm caudal to the abducens nuclei. Contralaterally directed slow phases were evoked from one animal in about one-third of the penetrations at the lateral extremes, probably near the entry zone of the vestibular nerve.

The injection sites were chosen from the maps of slow-phase velocity. The region where stimulation caused the greatest slow-phase velocity, or equivalently had the lowest threshold, were assumed to be the area in the NPH-MVN complex that was most involved with

the generation of eye movements. On this basis, injection sites were chosen symmetrically opposed on either side of the midline as indicated by the asterisks in Fig. 2.

Location and histological effects of chemical lesion

The locations of the injection sites were readily identified as the tips of the cannula tracks outlined by gliosis and containing mononuclear cells, macrophages, and microglial cells (see photomicrographs of Fig. 3). A composite reconstruction of the injection sites from all four monkeys is shown in Fig. 4. Each panel is a tracing from transverse sections cut in the plane of the electrode tracks spaced 0.5 mm apart in monkey 4. Because of the 0.5 mm spacing, the location of an injection site could be shifted as much as 0.25 mm rostrocaudally. Although 22 injections were made in the four monkeys, only 12 sites are indicated because of the overlap in repeated injections made at approximately the same coordinates.

The most rostral injection was in the caudal tip of the left abducens nucleus. The remaining sites extended 2.0 mm caudal to the abducens nuclei. The cannula penetrations generally ended within the MVN-NPH complex, but

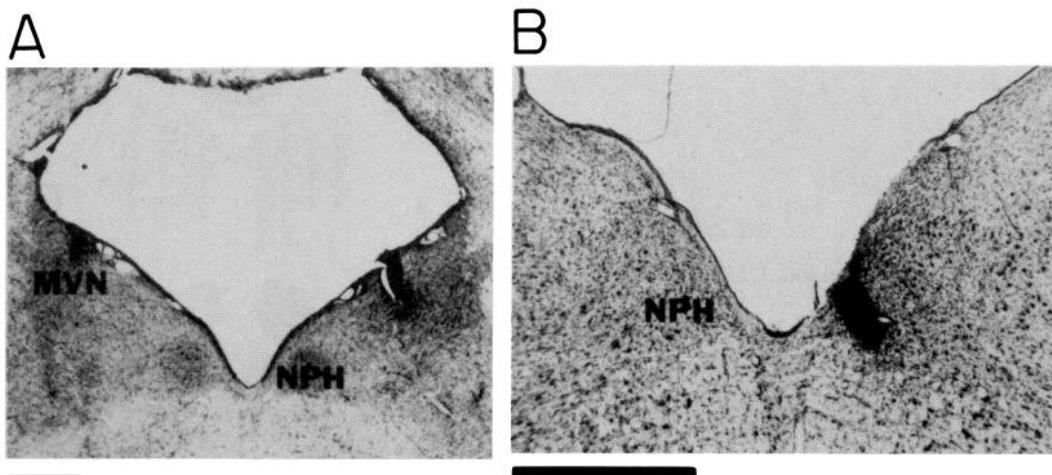


FIG. 3. Photomicrographs showing cannula tracks terminating at injection sites. *A*: transverse section 2.1 mm caudal to the abducens nuclei showing bilateral lesion sites in the medial vestibular nucleus (MVN) of monkey 2. *B*: lesion in the nucleus prepositus hypoglossi (NPH) of monkey 4. This transverse section was 1.0 mm caudal to the abducens nuclei. The contralateral lesion was 0.2 mm more rostral. Solid bars indicate 1.0 mm. Kainate injections at the sites shown in both *A* and *B* caused similar oculomotor deficits.

two extended into the parvocellular region of the reticular formation. Mediolaterally, the injection sites extended from 0.25 mm off the midline to the medial aspect of the lateral vestibular nucleus.

The majority of the permanent lesions were limited to these tracks of gliosis. At three injection sites, however, including the one in the abducens nucleus, a spherical region of cell loss and gliosis with an average diameter of 500 μm was found. In two cases kainate had been injected, ibotenate in the third. The kainate and ibotenate lesions were histologically indistinguishable. These regions were well demarcated with normal-appearing neurons immediately adjacent. The majority of injections, at levels close to life threatening, did not cause cell death in this region of the brain stem.

Behavioral effects of chemical lesions

GENERAL OBSERVATIONS. All of the injections were made bilaterally in fully alert monkeys. Within 2 min of the first of a pair of bilateral injections, the eye movements began to show pathological changes. These effects increased to a plateau within 2 h but within 4–12 h signs of recovery began and after some sessions the animal was behaviorally normal within 3 days. Because of this recovery, repeated injections were made in the same monkey at approximately the same coordinates. A total of 11 pairs of bilateral injections were made in four monkeys. All of the injections in *monkey 1* were phosphate-buffered ibotenate. In the first three sessions 10, 10, and 15 μg of ibotenate were injected bilaterally, but no motor abnormalities were observed. For the fourth and fifth sessions 30 μg were injected bilaterally at approximately the same coordinates and the pattern of features described below evolved. In an attempt to make more enduring lesions, 2–4 μg of kainate were injected at each site in the remaining three monkeys. The effects were similar for all the injections in all four monkeys, despite small differences in the injection sites. For repeated injections in the same animal, the same nature and degree of oculomotor impairment was established acutely. The time course of recovery was not systematically longer for successive injections. Thus even though reinjection was performed within 48 h, a cumulative toxic effect could not be produced. Instead, the re-

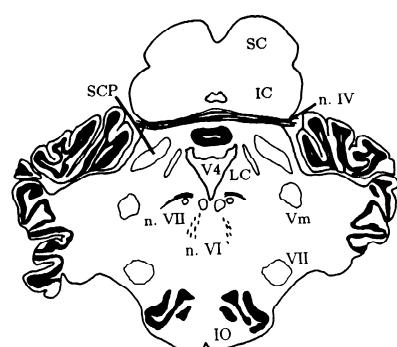
covery depended on the idiosyncrasies of a particular injection. As described below, in one monkey the degree of oculomotor recovery was less complete than in the others and the deficits persisted until the animal was killed 2 wk after the last injection.

Aside from oculomotor abnormalities, the most consistent and striking finding was truncal ataxia. When returned to its cage (within 2 h of injection) the animal would usually sit leaning against one side of the cage with obvious body sway. Typically it could not sit without leaning against the cage or using its hands for support. The severity of the truncal ataxia, out of proportion to limb ataxia, was exemplified by *monkey 2*. With its body steadied against the cage, *monkey 2* could quickly and accurately grab small pieces of apple with either hand. If, however, it attempted to drink from the water bottle, the monkey could not steady its body to keep its mouth on the nipple of the bottle. In most cases by 24 h after injection truncal ataxia was limited to a mild sway when the monkey sat without using his arms for support. None of the monkeys developed persistent head or body turning; recall that all injections were bilateral.

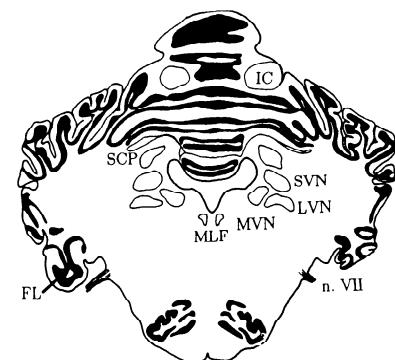
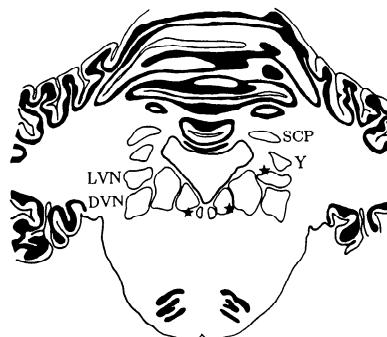
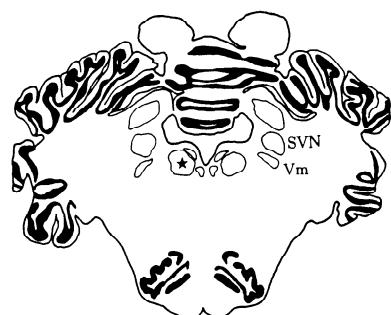
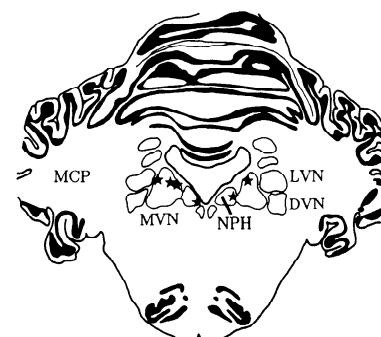
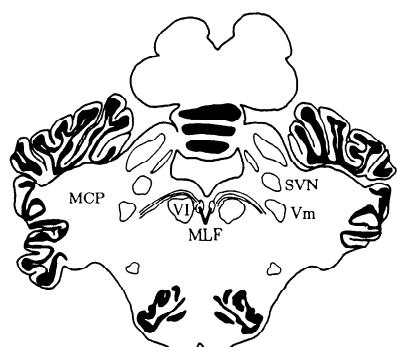
The second most frequent nonoculomotor effect was accumulation of saliva presumably due to difficulty in swallowing. On two occasions it was necessary to administer 0.3 mg of atropine intramuscularly to decrease the risk of aspiration of secretions. On a few occasions two monkeys vomited within 30 min of injection. Distinctly abnormal chewing behavior occurred for the first 12 h after about half of the injections. While the animal was awake, it would make rapid, repetitive, chewing movements at a rate of 3 Hz. Somewhat less common were paroxysms of prolonged yawning. Only one animal developed respiratory difficulties severe enough to require transient ventilatory support from a respirator. No animals developed generalized tonic-clonic seizures.

Death from injection of neurotoxin occurred in only one animal. *Monkey 3* received bilateral injections of 2 μg of kainate. It developed truncal ataxia, lip smacking, chewing automatisms, and the eye movements degenerated to complete ophthalmoplegia. During the first 4 h after injection, the monkey's breathing was regular. Nevertheless it was

ROSTRAL



5 mm



CAUDAL

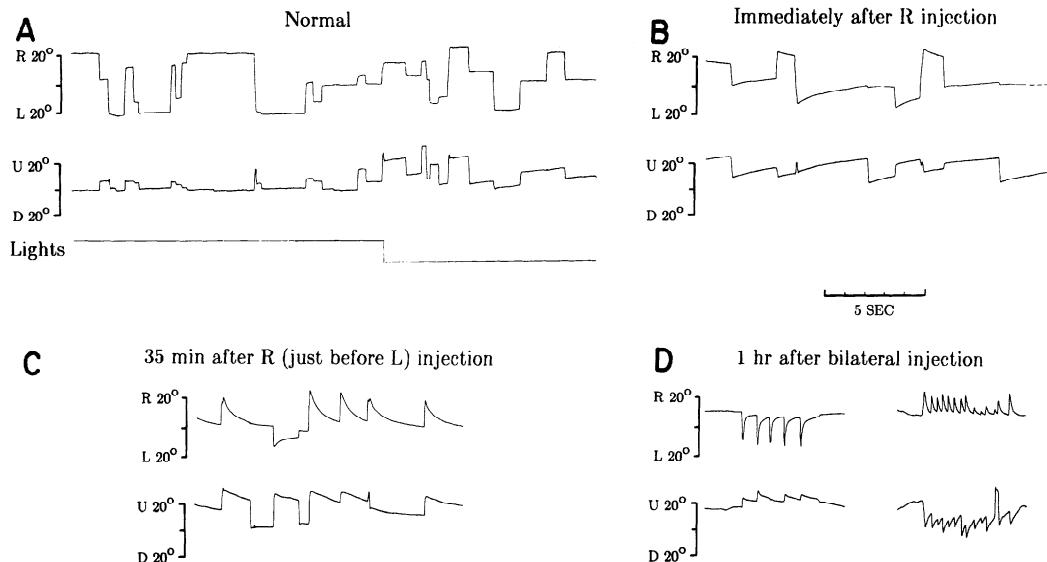


FIG. 5. Saccadic eye movements before and after injection. Horizontal eye position is on *upper trace*, vertical on *lower*. *A*: target-directed and spontaneous saccades recorded from a normal monkey. In the first half of the record the fixation target was alternated between right and left 20°. For the second half, spontaneous cyc movements were recorded in total darkness. Notice that even in total darkness horizontal gaze holding is steady. The upward drift in darkness is a form of downbeat nystagmus found in many normal rhesus monkeys. *B-D*: each panel shows spontaneous saccades recorded in total darkness from the same monkey as in *A* at various times after the injection of 30 µg of ibotenate as indicated. The records in *D* are 2 excerpts from a continuous record to demonstrate that eye position drifts centripetally after both leftward and rightward saccades. The time constant of the horizontal drift decreases progressively from 2 to 0.6 to 0.2 s in *B-D*. *A-D* were recorded at the same time scale as indicated. R, L, U, D are right, left, up, and down.

found dead in its cage the next morning. The cause was not pathologically determined, but was most likely either neurogenic respiratory arrest or asphyxiation secondary to aspiration. From this unfortunate result we conclude that the amounts of the injections could not have been increased without a significant fatality rate.

Oculomotor effects

GAZE HOLDING. Target-directed and spontaneous eye movements recorded from a normal monkey are shown in Fig. 5*A*. In the first part of the record the monkey fixated targets

that were alternated between right and left 20° in a dimly lit room. Subsequently all lights were extinguished, and spontaneous saccades were recorded in complete darkness. Horizontal gaze was steady in both conditions. Between saccades there were no slow drifts. The neural integrator was "perfect" or without a noticeable decay or leak in its output. The eye-position command from an impaired or leaky integrator decays with time which causes the eyes to drift exponentially toward a null position. This is the position where the drift velocity is zero. When gaze-evoked nystagmus is present, the direction of the drift is always

FIG. 4. Serial brain stem sections showing the locations of the injection sites. Each *inset* is a tracing from *monkey 4*. The drawings are from sections spaced 0.5 mm apart from the level of the rostral end of the abducens nuclei through the rostral medulla. The locations of the injection sites are indicated by the stars and are superimposed from all 4 monkeys. Abbreviations: DN, dentate nucleus; DVN, descending vestibular nucleus; FL, flocculus; IC, inferior colliculus; IO, inferior olive; LC, locus ceruleus; LVN, lateral vestibular nucleus; MLF, medial longitudinal fasciculus; MCP, middle cerebellar peduncle; MVN, medial vestibular nucleus; NPH, nucleus prepositus hypoglossi; n. IV, trochlear nerve; n. VI, abducens nerve; n. VII, facial nerves; SC, superior colliculus; SCP, superior cerebellar peduncle; SVN, superior vestibular nucleus; Vm, motor nucleus of the trigeminal; V4, fourth ventricle; VI, abducens nucleus; VII, facial nucleus; Y, y-group of the vestibular nucleus.

toward the null point, which may or may not correspond to the primary or straight ahead position. The degree of leakiness is quantified as the time constant, T_n , of the exponential drift which can be computed as

$$T_n = -\frac{E - E_{\text{null}}}{\dot{E}} \quad (1)$$

where E is the current eye position, E_{null} is the null position toward which the eye is moving, and \dot{E} is the current velocity of the drift. Figure 5A shows that the horizontal drift velocity was essentially zero and the integrator time constant infinitely large in the preinjection state. In the vertical direction (Fig. 5A second trace) the eye position was steady in the light but drifted upward when the animal was in darkness. This is only an example of a weak downbeat nystagmus that is found in many normal rhesus monkeys.

Figure 5, B-D shows gaze-holding failure in the same monkey at various times after the injection of ibotenate. Since only one cannula could be advanced through the recording chamber at one time, the paired bilateral injections were separated by ~ 30 min. Immediately after a 30- μg injection in the region of the right MVN and NPH, failure of horizontal gaze holding occurred in both the ipsi- and contralateral directions (Fig. 5B). The time constant for this degree of leakiness was ~ 2 s, significantly reduced from the normal value of 20 s or greater. For vertical eye movements, only the normal downbeat nystagmus seen in the dark was present; the integrator for vertical eye movements was not yet significantly impaired. Fig. 5C shows that 35 min after the unilateral injection the time constant for horizontal eye movements decreased further to 600 ms. Postsaccadic drift for vertical eye movements had a time constant of 4 s. A few minutes after this, 30 μg of ibotenate was injected into the contralateral side. Gaze holding progressively worsened until the monkey could not hold its eyes away from the null point for any significant length of time (Fig. 5D). In the horizontal direction the time constant of postsaccadic drift was 200 ms. These eye movements simply reflect the viscoelastic relaxation of the muscles and other orbital tissues after a burst of innervation, the eye-velocity command with no accompanying eye-position signal. Since the net time constant of postsaccadic drift had approached the mini-

mum of 200 ms imposed by the viscoelastic properties of the eyeball, T_n of the integrator must have been significantly <200 ms. For all practical purposes the neural integrator had been ablated. At this point the integrator for vertical eye movements was quite deteriorated as well. It was, however, less severely impaired because the time constant for the vertical drifts in Fig. 5D was ~ 750 ms.

The same general pattern of gaze-holding failure occurred in all 11 bilateral injections in all four monkeys. The time constant for horizontal, postsaccadic drift decreased to the same minimum set by the mechanical properties of the orbit. The mean and standard error of the mean were 0.227 ± 0.008 s (n equals 56, determined from 5 consecutive saccades at the height of the effects of each injection), which means that the integrator for horizontal eye movements was consistently and completely disabled. The small variability is thought, due to the mean, to reflect orbital mechanical properties that presumably do not differ among monkeys. There was variability in the rate at which gaze holding deteriorated. Total integrator loss could develop before the completion of the first injection or take as long as 1 h (Fig. 5D) to occur. Most importantly, for some injections there was total loss of integrator function for horizontal eye movements after the first of a pair of injections; that is, even while the lesion was presumably still unilateral.

Gaze holding for vertical eye movements was less severely impaired. As shown in Fig. 5, failure of vertical gaze holding lagged the onset of horizontal postsaccadic drift. The minimum time constant for vertical postsaccadic drift was always larger than that for horizontal. The vertical time constant, measured at the same time and averaged over the same experiments as for the value reported above for the horizontal system, was 2.52 ± 0.25 s. The standard error of the mean is thought to be larger because the leakiness of the vertical system did not encroach upon the minimum of ~ 200 ms determined by the mechanics of the orbit. The range of these time constants was 0.39–4.6 s. Unlike the case for horizontal eye movements, there was still an appreciable degree of vertical integration when horizontal integration had gone.

As mentioned previously, the effects of toxin injections were not permanent. Recovery of

integrator function for *monkey 2* is shown in Fig. 6. The horizontal time constant is plotted for various times after bilateral injections of kainate. The longest impairment occurred after *injection 4* when the time constant remained below 3 s for a week. There was no permanent cumulative effect from successive injections. Recovery from *injection 2* was more rapid than from *injection 1*, and recovery from *injection 3* was even more rapid. The lack of a lasting functional deficit correlates with the absence of extensive neuronal cell loss on histological examination.

When the neural integrator for horizontal eye movements was severely damaged, (e.g., Fig. 5), the ability to maintain eccentric gaze was not improved by turning on the room lights. With less severe gaze-evoked nystagmus, either during the onset of or recovery from the lesion, the velocity of postsaccadic drift was attenuated when the lights were on. For example, in *monkey 2* 6 days after a bi-

lateral kainate injection, the time constant of postsaccadic drift in the dark was 2.2 s, whereas in the light it was 6 s. These values correspond to drift velocities, when the eye is 20° from the null position, of 9.1 and 3.3°/s, respectively. Visually induced suppression of postsaccadic drift was quantifiably detectable during recovery after every injection. An obvious attenuation in postsaccadic drift with illumination was most evident when the integrator had partially recovered such that its time constant was between 1 and 10 s. Thus, through some visual gaze-stabilization mechanism, the animals were able to attenuate postsaccadic drift despite an impaired neural integrator.

Rebound nystagmus was observed in every animal as soon as it had recovered the ability to maintain eccentric gaze for several seconds. This was characterized first by a dampening, in the light, of gaze-evoked nystagmus at an eccentric eye position held for, say, 10 s. Then,

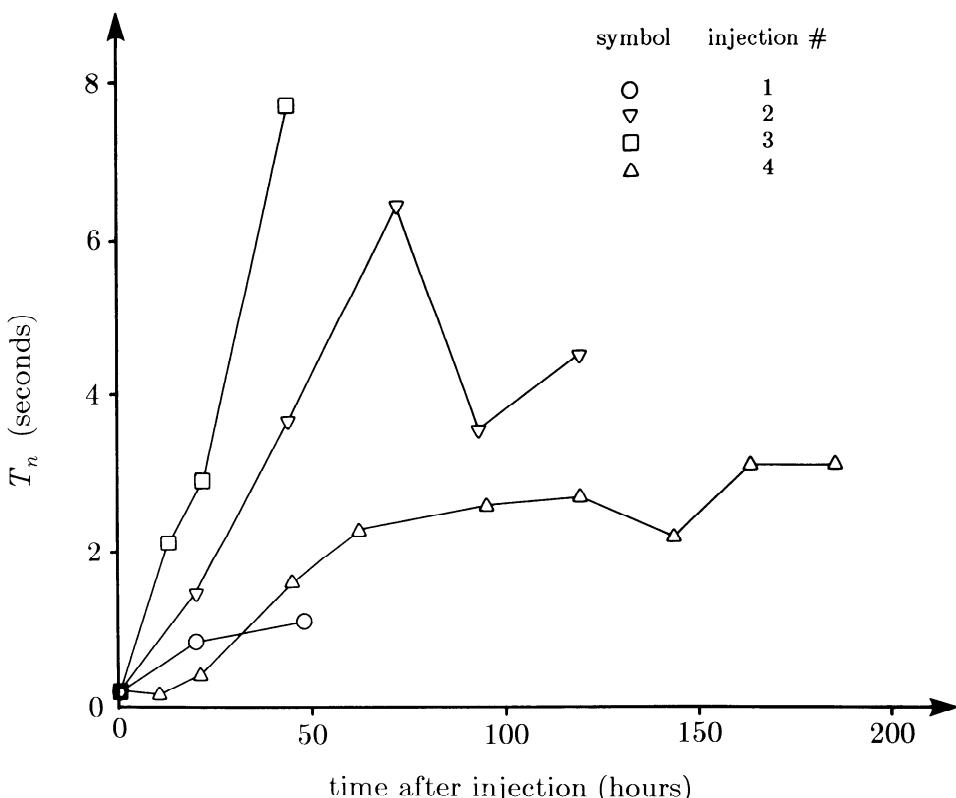


FIG. 6. Recovery of integrator time constant. The time constant, T_n of horizontal, postsaccadic drift in the dark measured at various times after each of the 4 bilateral kainate injections in *monkey 2* are shown as a function of time.

on return to the null position, a transient rebound nystagmus occurred with slow phases directed toward the side of prior eccentric gaze.

As demonstrated in Fig. 5, the null position did not always correspond to the primary or straight-ahead position. After the first of a pair of injections the null point typically shifted ipsilaterally toward the side of the initial injection by $\sim 10\text{--}20^\circ$. When the contralateral injection was made, the null point shifted back toward the primary position (usually within 5°), or in other words, again in a direction ipsilateral to the side of the most recent injection. In 9 out of 11 initial injections of a bilateral pair, the null point drifted ipsilaterally. For the other 2 injections (in 2 different animals) the null point shifted ipsilaterally transiently and then moved contralaterally before the second injection of the bilateral pair. For 7 of 11 cases the second injection caused the null point to move ipsilaterally (with respect to the second injection) back to near the midline. In 4 of 11 cases this injection caused a transient ipsilateral shift in null point followed by a sustained contralateral shift. On a longer time scale, the null point also shifted during recovery. Within the first few days after a lesion it could deviate by as much as $20\text{--}30^\circ$. Although this shift was always to only one side or the other, it followed no consistent pattern with regard to the side of the first or second injection.

VESTIBULOOCULAR REFLEX. The vestibuloocular reflex (VOR) was tested by rotating the monkey en bloc about an earth-vertical axis in total darkness. Figure 7A shows the horizontal eye position, eye velocity, and chair velocity as a function of time in a normal monkey during a constant-velocity step of chair rotation. The slow-phase velocity of perrotatory nystagmus decayed exponentially with a time constant of 19.6 s. At the end of the rotation a braking deceleration caused postrotatory nystagmus in the opposite direction. Within minutes after bilateral injections, the response in every animal to a step of rotation was a small step change in eye position of $3\text{--}5^\circ$ in the opposite direction. The step change in eye position for the same velocity of chair rotation became progressively larger with recovery. Twenty-four hours after a kainate lesion in monkey 2, the VOR for the same rotation used in Fig. 7A is shown in Fig.

7B. The change in eye position had the waveform that the envelope of the slow-phase eye velocity would normally have. The eye position appeared to be determined solely by the head-velocity signal produced by the semicircular canals. There was no neural integrator to convert the initial step increase in the head-velocity signal into a ramp increase in eye position. Consequently there were no slow phases of vestibular nystagmus. The brief dips in eye position were attempted saccades. In the absence of an integrator, each attempted saccade or quick phase was followed by a rapid return (similar to those in Fig. 5D) to the offset position determined by the canal signal as illustrated schematically in the lower trace of Fig. 7.

Relative to the condition just after a lesion, this larger deviation in eye position for the same head velocity (Fig. 7) implies that the gain of the direct pathway of the VOR that conveys the eye-velocity signal to the motoneurons had increased appreciably, but the neural integrator time constant had not. In general the amplitude of the eye position deviation increased with increasing head velocity. However, this relation was not quantified because for small head velocities the amplitude of the position deviation was comparable to the size of small spontaneous shifts in the null position and for large head velocities resetting saccades interrupted the development of the full step in eye position (that is, a clearly defined peak eye deviation where the eye velocity was zero was not attained). VOR responses similar to that of Fig. 7B were recorded within the first 24 h after a lesion of 6 of 11 injections. In four other instances recovery had progressed such that at the time of the first vestibular testing, vestibular nystagmus with markedly curved slow phases was observed. This latter response represents a later stage in the continuum of recovery compared with the situation shown in Fig. 7B. One animal died before postinjection vestibular recordings were scheduled. Thus, just as with saccades, loss of the neural integrator caused eye position (Fig. 7B top trace) to follow the time course that would normally be followed by eye velocity (Fig. 7A middle trace).

The time constant of the per- and postrotatory response was also impaired. The time constant of the vestibular signal sent to the motoneurons was no longer increased cen-

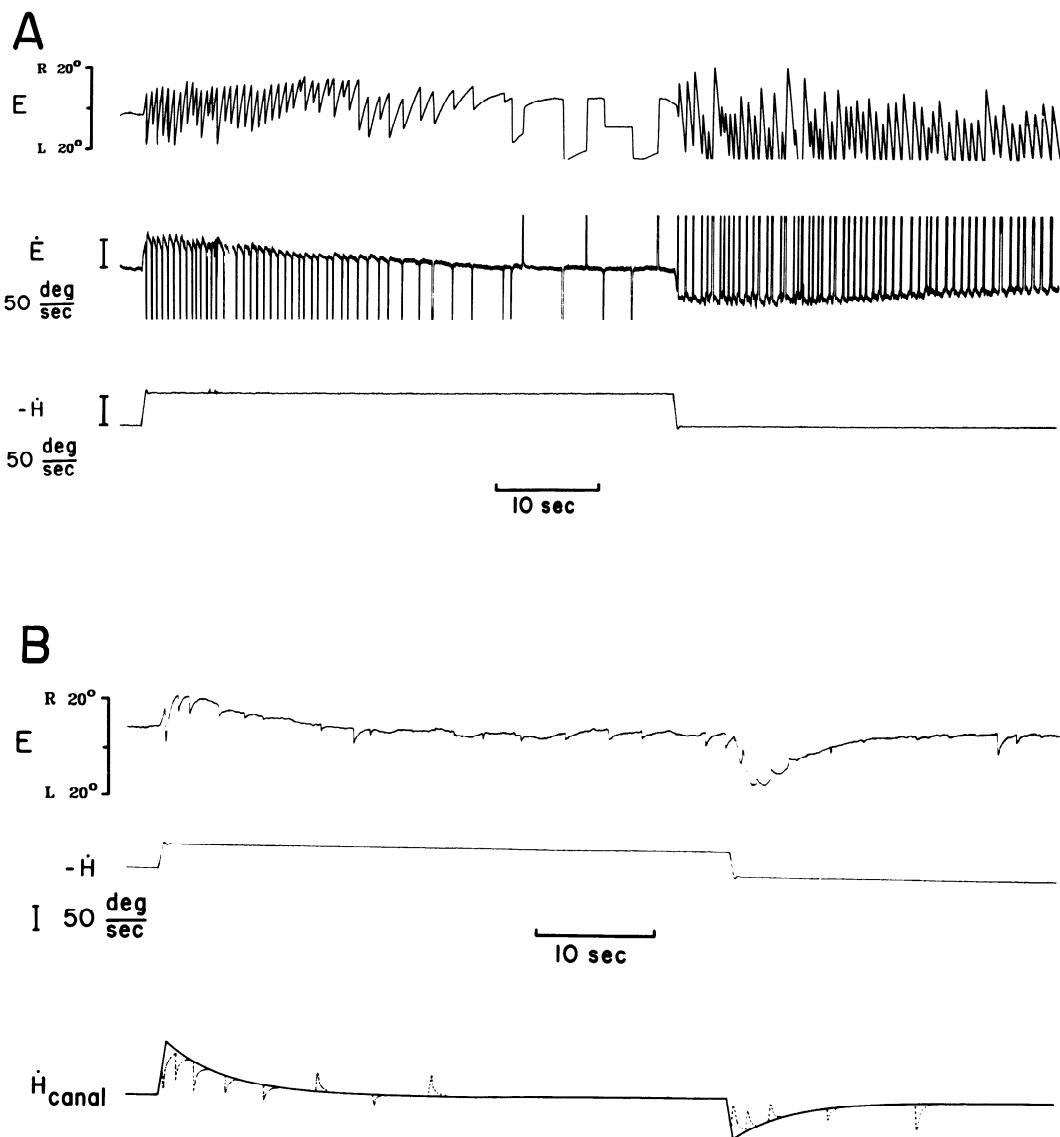


FIG. 7. Vestibuloocular reflex before and after injection of kainic acid. *A*: eye position, E; eye velocity, \dot{E} ; and head velocity, \dot{H} ; recorded during en bloc rotation in total darkness in a normal monkey. *B*: eye position recorded from the same monkey during the same vestibular stimulation 1 day after bilateral injections of kainate. A hypothetical canal signal is shown at the bottom with superimposed saccades as they would appear in the absence of a neural integrator (dashed lines).

trally, a phenomenon called velocity storage (29), to its normal value of 16–20 s; instead the head-velocity signal decayed with a time constant of 6 s, which is comparable to the value reported for the cupula alone (14). Thus the lesion also abolished vestibular velocity storage. Although both impaired velocity storage and neural integrator failure occurred after most injections, there were cases for which the

time constant of per- and postrotatory vestibular nystagmus was clearly >16 s despite a neural integrator time constant <2 s. On the other hand, there was never a case of decreased vestibular velocity storage without a severely impaired neural integrator. These results suggest that the region of the MVN and NPH affected by these injections is crucial for the normal operation of the neural integrator

whereas vestibular velocity storage is dependent on nearby regions.

OPTOKINETIC RESPONSE. Eye movements produced by full-field optokinetic stimulation in a normal monkey are shown in Fig. 8A. After several seconds the slow-phase eye velocity nearly equals drum speed, and after nystagmus continues when the light is extinguished due to optokinetic velocity storage. Although the monkeys made eye movements in response to vestibular stimulation at the height of the effects of the injection, optokinetic responses were typically absent until several hours after the injection. The eye position recorded 1 day after a kainate injection is shown in Fig. 8B. The eye position trace had the time course that the eye-velocity record would normally have. The change in eye position again reflects a step input command with superimposed quick phases. The new position or null point is the point to which the eye returns after each quick phase. The step of eye-velocity command generated by the

optokinetic system was not converted by the neural integrator to a ramp of eye position (normal slow phases). The velocity of the rapid return back to the new null point after each saccade was independent of the drum speed; it was not a true slow phase of nystagmus, but was determined by the leakiness of the neural integrator, just as in Fig. 5D.

The recovery of optokinetic nystagmus paralleled that of the vestibular system. Initially only a small step change in eye position was elicited from optokinetic stimulation. Within the first day of recovery larger step deviations like that of Fig. 8B were recorded after 6 of 11 lesions. For the other injections recovery had already progressed to the generation of optokinetic nystagmus (as the former 6 did in time) with exponentially curved slow phases.

Figure 8B shows that when the light was extinguished the eye did not immediately return to its base-line null point, which implies that the velocity storage mechanism of the optokinetic system, responsible for generating

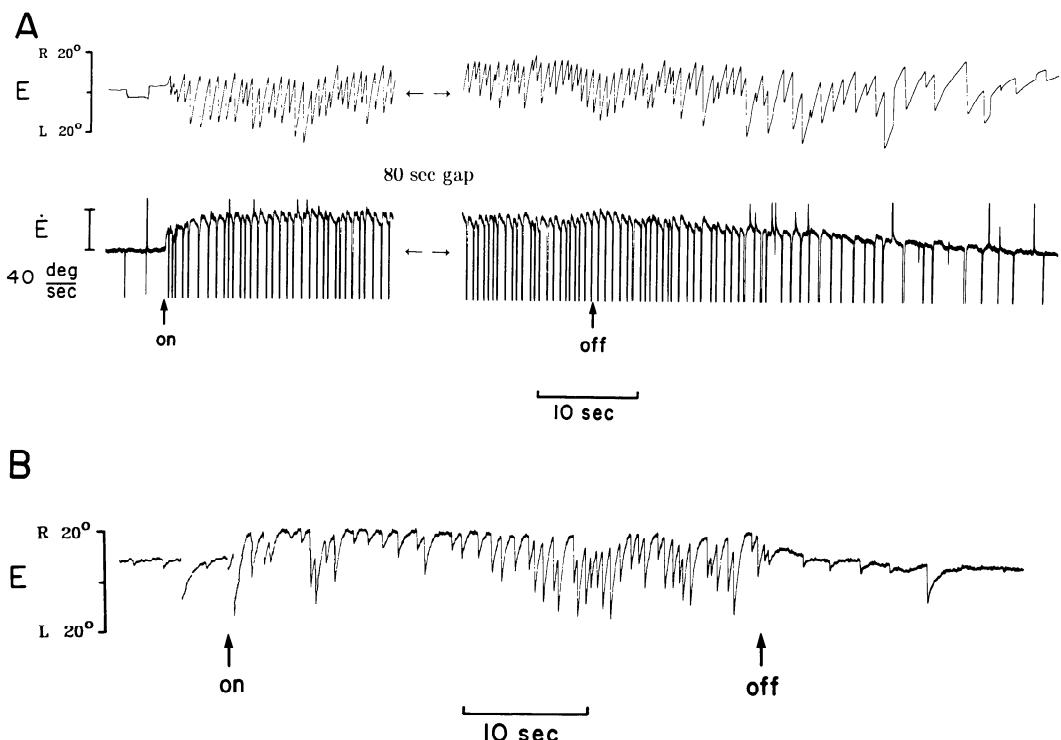


FIG. 8. Optokinetic response before and after injection of kainic acid. *A*: eye position and eye velocity response in a normal monkey. Arrows indicate the onset and offset of the light. *B*: change in eye position recorded 1 day after a kainate injection; see text for details. Drum velocity is $40^{\circ}/s$ to the right in *A* and $75^{\circ}/s$ in *B*.

normal optokinetic after-nystagmus, must have been excited. The velocity storage, however, had an abnormally small time constant of 3.5 s in this case, compared with its normal value of ~16 s. The recovery of the time constant of optokinetic after-nystagmus, vestibular per- and postrotatory nystagmus, and of the neural integrator are shown for *injection 4 of monkey 2* in Fig. 9. The first measurable velocity storage for optokinetic eye movements occurred 42 h after injection, whereas the time constant for vestibularly induced eye movements could be quantified 20 h after injection. The time constant for the vestibular system was always >5 s since it is, in part, determined by the mechanics of the peripheral sensory apparatus and is independent of any central storage. There were optokinetic responses for which the eye position deviation returned to zero much more rapidly than that shown in Fig. 8B when the light went out. In other words, the time constant of optokinetic storage, produced entirely by central mechanisms, did decrease all the way to zero. As shown in Fig. 9, once the time constant of optokinetic storage approached that of vestib-

ular velocity storage, the two continued to recover more or less together, supporting the general belief that velocity storage is common to the two systems.

PURSUIT. Acutely after bilateral injections the monkeys were too impaired to attempt to smoothly track small targets. Eye movements were elicited instead through the use of large-field stimuli. Figure 10A shows the first few seconds of the eye-position response during constant-velocity, full-field optokinetic stimulation in a normal monkey. The normal eye movement at the onset of illumination of an already rotating optokinetic drum is a ramp change in eye position whose slope nearly equals the drum velocity, i.e., a step change in eye velocity. This initial component of the optokinetic response in foveate animals is thought by many to be generated by the pursuit system (33). For example, in patients (43) or flocculectomized monkeys (45) with deficient pursuit, but preserved optokinetic responses, the buildup of slow-phase velocity is gradual as it is with afoveate animals like the rabbit in which a pursuit system is absent.

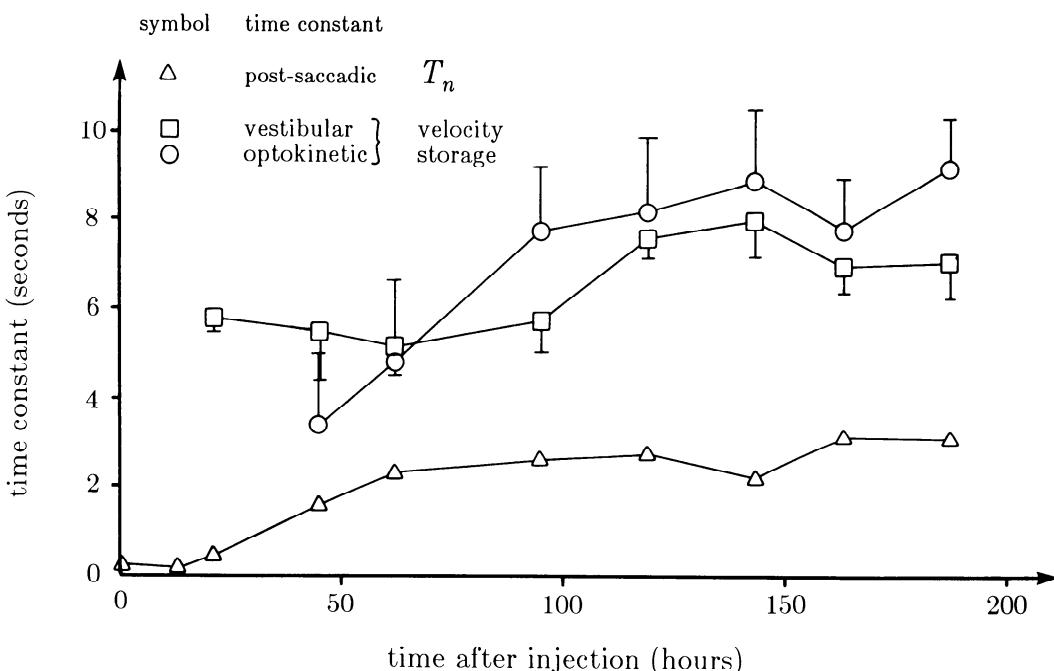


FIG. 9. Time course of recovery of time constants for vestibular and optokinetic afternystagmus (velocity storage) and the neural integrator. Error bars indicate the standard error of the mean. Typically, 6 trials in *monkey 2* were averaged for each point.

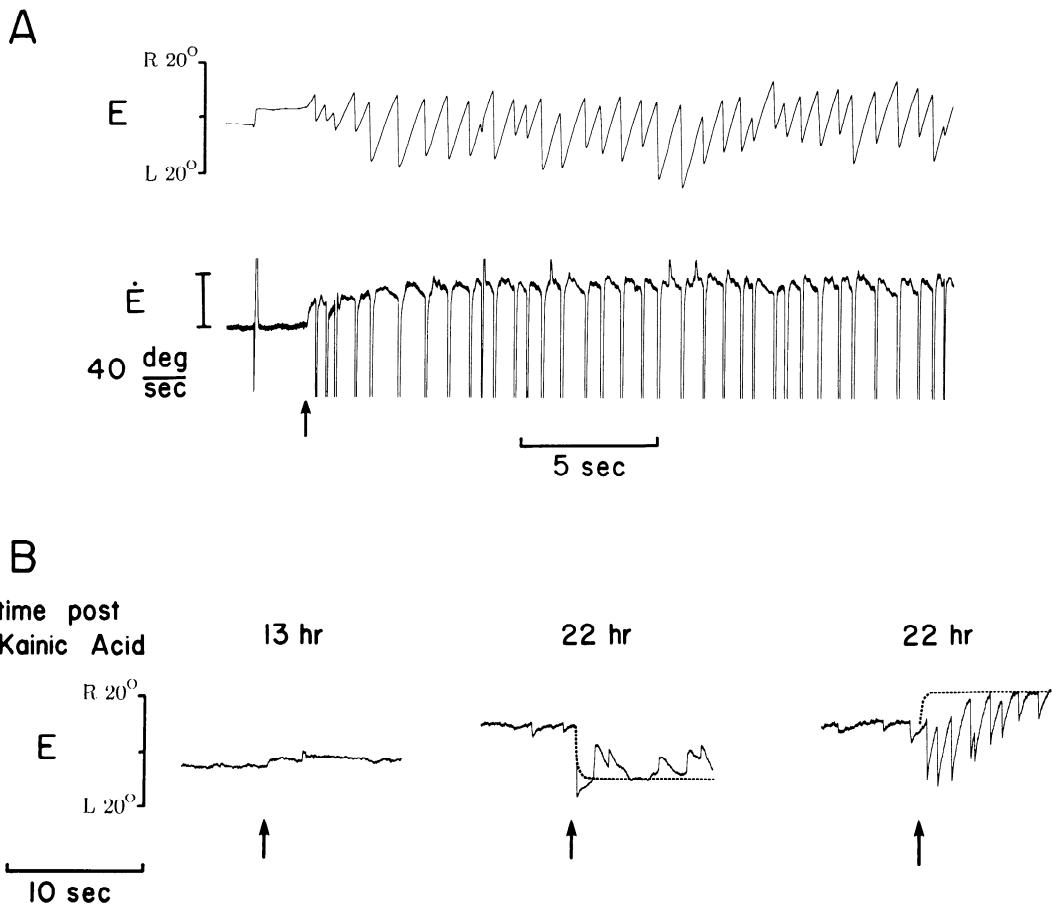


FIG. 10. Initial component of optokinetic response before and after injection of kainic acid. *A*: eye position (E) and eye velocity (\dot{E}) as a function of time in a normal monkey. Drum velocity was 40°/s to the right. *B*: eye position traces at 13 and 22 h after a kainate injection. Arrows indicate the onset of light at which time the null position shifted in a stepwise fashion in the direction of drum motion. This response was usually obscured by quick phases followed by a rapid return to the new null position (dotted lines) as in Figs. 7 and 8. There are no slow phases of optokinetic nystagmus. Drum velocity in the 3 records was 40°/s to the right, left, and then right.

The initial component of the optokinetic response at various times after an injection is shown for the same monkey in Fig. 10*B*. In all three cases it was a step change in eye position. Just as with the vestibular and optokinetic responses (Figs. 7 and 8), the change in eye position again reflected the eye-velocity signal. There was no integrator to convert the velocity-step command into a ramp signal. In the two records at 22 h the animal had recovered the ability to generate quick phases, but, just as in Fig. 5*D*, after each one the eye returned rapidly (with a velocity that was independent of drum speed) to the new position or null point determined by the eye-velocity

signal. This is particularly evident in the middle record. When the light came on, the monkey just happened to make a saccade that was larger than the offset in the null point so that the eye actually drifted back initially, toward the new null point in the direction opposite to that of the drum motion.

After ~12 h of recovery, this monkey could pursue a small illuminated target. Figure 11 compares pursuit movements recorded prior to (Fig. 11*A*) and 22 h after (Fig. 11*B*) bilateral kainate injections. The time constant of the neural integrator in (Fig. 11*B*), determined from postsaccadic drift in darkness, was 0.44 s, and the null position was approximately 3°

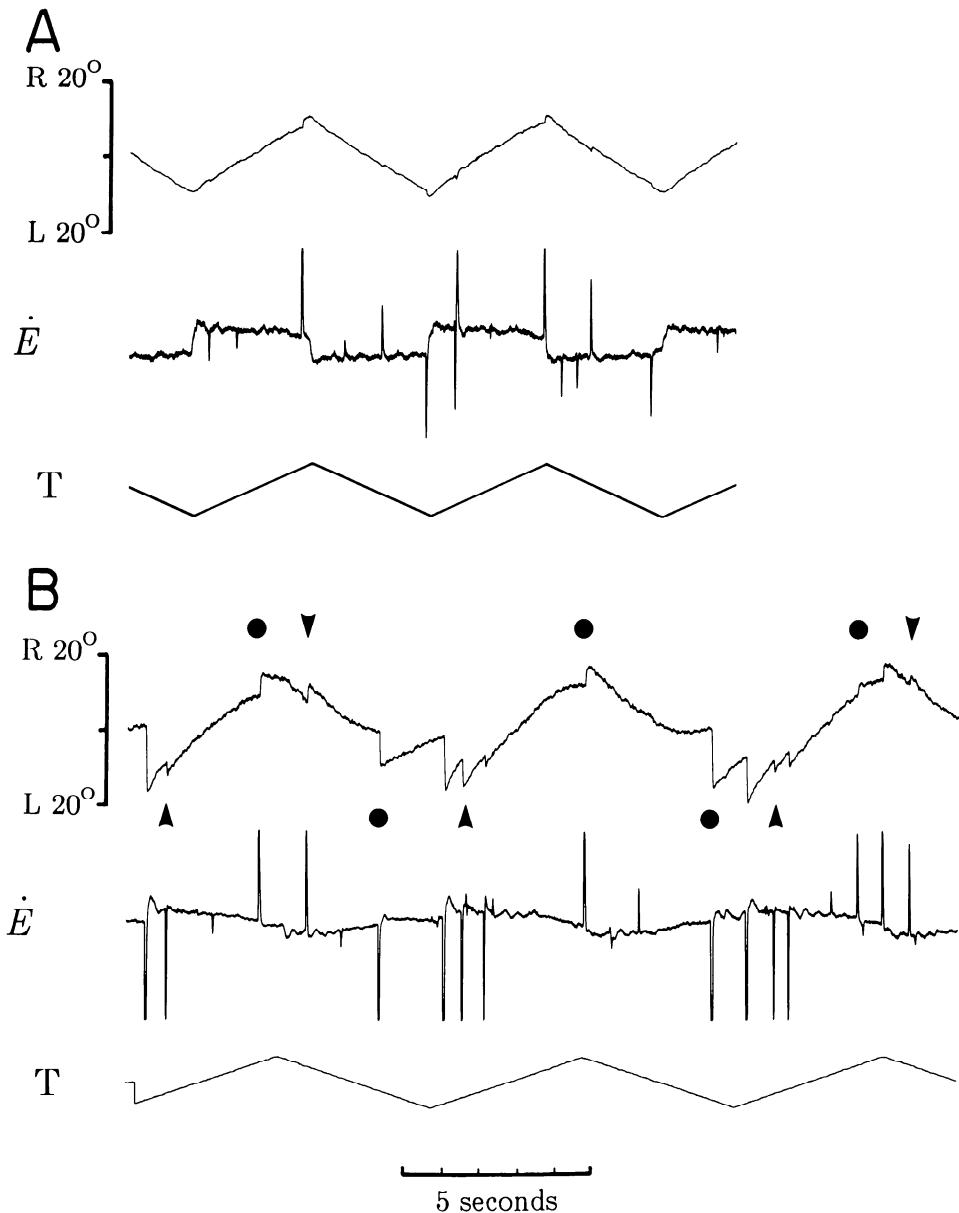


FIG. 11. Pursuit eye movements before and after injection of kainic acid. *A*: eye position, eye velocity (\dot{E}), and target position (T) recorded in a normal monkey during smooth pursuit of a small target moving in a triangular waveform. *B*: eye movements recorded during the same task 22 h after the injection of kainate. Null point is close to zero. When the eyes move centrifugally, catch-up saccades are needed (filled circles); when centripetally, back-up saccades occur (arrows).

to the right. When the eyes were moving toward the null position from either the left or the right (arrows, Figure 11B), "back-up" corrective saccades were required to stay on target. Conversely, when the monkey was tracking

the target away from the null position (circles, Fig. 11B), "catch-up" saccades were required. Figure 11 also illustrates that in the presence of visual feedback, the oculomotor deficits produced by a very leaky neural integrator (T_n

was only 0.44 s) may appear to be quite small relative to the degree of postsaccadic drift in darkness.

DISCUSSION

Stimulation

Predominantly horizontal nystagmus with ipsilateral slow phases (Fig. 2A) was elicited by stimulating in the region of the rostral poles of the MVN and NPH. The preponderance of ipsilateral slow phases was initially surprising since it is well known that stimulation of the nerve coming from a horizontal semicircular canal causes contralateral slow phases (10). Since this nerve ramifies in the rostral MVN, it was expected that stimulation there would produce a similar result. Given the complexity of type I and type II neurons in this structure, this expectation was premature. There are earlier reports of contralateral slow phases evoked from the region of the VN. However, in those studies the monkeys were anesthetized and cervically transected at the C₁ level; bipolar electrodes were used, and currents 10⁴ times greater than those used here were applied. Tokumasu et al. (37) found that the direction of the slow phases could depend on stimulation parameters. Again, however, the monkeys were anesthetized and the currents were still an order of magnitude larger than used here. It is very likely that the difference in this study from previous ones is that the monkey was not anesthetized allowing current densities to reach levels that had localizing values. Anesthesia would also considerably disrupt the ability of downstream structures to respond normally to the stimulation.

The uniform distribution of the slow-phase direction shown in Fig. 2B, within the VN complex suggests that with stimulation in the alert animal, type II vestibular neurons were preferentially activated over type I cells. There is a powerful inhibitory commissural system linking the vestibular nuclei across the midline (34, 35). It carries axons of type I fibers from the contralateral nucleus that excite type II neurons in the ipsilateral nucleus that in turn inhibit type I neurons ipsilaterally. If these commissural fibers were activated (electrical stimulation excites fibers preferentially over neurons) ipsilateral type I fibers would be in-

hibited and, through an axon reflex contralateral, type I, efferent axons would be excited thereby producing an ipsilateral eye movement. Moreover, a major input to the NPH is excitation from the contralateral VN (2) and stimulation of these fibers could have similar results. Whatever the reason, we found consistently that stimulation of the VN and NPH in the alert monkey, at least at 20 μ A, caused ipsilateral slow phases.

Histological reconstruction of lesion sites

The majority of the injections were in the rostral 2 mm of the MVN and NPH with a few outlying sites in the caudal tip of the abducens nucleus, reticular formation, and the medial border of the lateral VN as summarized in Fig. 4. Unfortunately ibotenate and kainate were not effective in killing neurons in this region. At only three injection sites was the extent of gliosis ($\sim 500 \mu\text{m}$ in diameter) larger than the diameter of the cannula. In the first monkey attempts to create more permanent lesions were made by increasing the amount of ibotenate injected. At physiological values of pH and temperature, however, it was not possible to achieve concentrations $> 10 \mu\text{g}/\mu\text{l}$, and an upper limit of 3 μl per injection was set empirically to reduce the possibility of creating large nonspecific lesions just from a large-volume pressure injection. Since the first monkey still recovered from such injections, a switch was made to the more potent neurotoxin, kainate.

Injections of kainate at a 1- $\mu\text{g}/\mu\text{l}$ concentration produce well-demarcated regions of cell loss in the rat striatum (11), but Henn et al. (20) found that concentrations of 4–8 $\mu\text{g}/\mu\text{l}$ were required to create permanent lesions in the monkey PPRF. One microliter injections of kainate at 2–4 $\mu\text{g}/\mu\text{l}$ were made at each site in the present study. Kainate appeared to be more potent than ibotenate in that the motor deficits developed more rapidly. One animal died from an injection of kainate at a concentration of 2 $\mu\text{g}/\mu\text{l}$. Because of this fatality, no concentrations of kainate $> 4 \mu\text{g}/\mu\text{l}$ were used. Even at the higher concentration, kainate still did not create permanent behavioral deficits, and a cumulative toxic effect could not be produced by reinjecting at the first signs of recovery. Consequently, the extent of the region of impaired neuronal function shortly af-

ter injection could not be ascertained directly. If an extrapolation is made from the effects on rat striatum, then a 1- to 2-mm diam sphere of parenchyma might have been affected. This would be compatible with the mild truncal ataxia observed suggesting a spread of the neurotoxin to the lateral VN but not too far into it and with the failure to observe a lateral rectus palsy indicating that the spread did not reach the abducens nuclei.

On the other hand, it should be noted that lesions were not placed far enough away from VN and NPH that the integrator was spared. This test remains to be done to insure directly that loss of integration is not the result of a broad, diffuse lesion anywhere in the caudal pons or rostral medulla. It is probable that with a pressure injection some of the neurotoxin leaked back up the cannula track and into the fourth ventricle where it might have been responsible for some of the nonoculomotor effects seen. It is even possible that this route could affect the neural integrator. We would guess that the concentration of the neurotoxin near the cannula tip would be at least an order of magnitude greater than in any other group of neurons in this region near the ventricle, such as the flocculus, known to have anything to do with eye movements and gaze holding. Nevertheless, control experiments to examine these possibilities need to be done.

Oculomotor deficits

OVERVIEW. The combined oculomotor deficits in the saccadic, vestibular, optokinetic, and pursuit systems could all be attributed to destruction of the neural integrator by the injection of neurotoxins in the region of the MVN and NPH. This constellation of eye movement abnormalities provides direct evidence in support of the hypothesis of the final common integrator. All rapid eye movements (saccades or quick phases) were followed by centripetal drifts toward a null position with an exponential time course that was governed by the viscoelasticity of the orbital mechanics. For slow eye movements, stimuli that generated a step velocity command for either the vestibular, optokinetic, or pursuit systems all caused a step change in eye position. There was no integrator to convert the step-velocity command into a ramp-position command. Consequently, in the absence of the neural in-

tegrator, the eye-position record had the time course that the eye-velocity tracing would normally have for all conjugate eye movements.

GAZE HOLDING. Figure 5 shows that lesions in the MVN and NPH damaged the integrator for horizontal eye movements more severely than for vertical. The encoding of vertical eye movements by the vestibular complex is concentrated in the superior subdivision. This nucleus projects to motoneurons in the oculomotor nuclei and premotor neurons in the interstitial nucleus of Cajal (24). It has been suggested that the neural integrator for vertical eye movements may be comprised of reciprocal connections between the latter nucleus and the superior VN (W. M. King, personal communication). Thus injections in the region of the MVN and NPH might be expected to primarily affect the integrator for horizontal eye movements. On the other hand, recordings from the NPH (2) show many neurons involved with vertical as well as horizontal eye movements, and it is the involvement of these neurons that probably caused the decrease in vertical integrator action.

The minimum time constant for postsaccadic drift is determined by the viscoelastic properties of the antagonist muscles and orbital fascia. To a first-order approximation, the muscle plant has a single time constant of 200 ms. Surgical ablation of the cerebellum in cat (31) and of the flocculus in monkey (45) does impair the neural integrator. However, in both patient data and previous chronic lesion studies, the time constant for postsaccadic drift was >1.3 s which is seven times longer than the time constant of the muscle plant alone. Therefore there must have been some residual leaky integration performed in the brain stem. Only lesions in the region of the MVN and NPH caused the time constant to decrease to 200 ms. This degree of integrator deficit occurred in all the bilateral injections for all four monkeys. Thus on the basis of eye movement data, lesions in the region of the MVN and NPH have produced the greatest impairment of integrator function observed from any site or type of lesion. The integrator time constant must have been <200 ms, a minimum beyond which further deterioration cannot be detected from measuring eye movements.

VESTIBULAR IMBALANCE AND THE NULL POSITION. Initially it was puzzling that after the first of a pair of injections the unilateral vestibular lesion did not cause intense nystagmus. Transsection of the vestibular nerve would do so with ipsilateral slow phases. On the other hand, since stimulation in the region of the MVN and NPH caused ipsilateral slow phases, one might expect a lesion there to create contralateral slow phases. That neither happened indicates that the situation is more complicated, and this is compounded in that we do not know how the neurons were reacting to the neurotoxins. No doubt their ability to react to incoming signals was disrupted so they can, for example, no longer perform integration, but their sustained discharge rates and the difference in the effect on excitatory and inhibitory neurons are quite unknown so it is premature to try and predict what sort of nystagmus would result from such lesions.

There is, however, another important factor. The slow phase of nystagmus is created by the neural integrator as it integrates a constant difference from a push-pull pair of semicircular canals. As shown throughout the RESULTS, without a neural integrator one cannot have nystagmus. Since a unilateral lesion alone can seriously cripple the integrator (the time constant in Fig. 5C was only 0.6 s) one can easily explain why nystagmus was not seen at such times despite a unilateral vestibular lesion. When the integrator is only partly leaky it is helpful to resort to analysis. In this case, the eye velocity, $\dot{E}(t)$, produced by unbalancing of the input of ΔR spikes/s to the neural integrator is approximately described by Eq. 2

$$\dot{E}(t) = G\Delta R - \frac{E(t)}{T_n} \quad (2)$$

Normally, T_n is so large that the drift due to the integrator leak, $E(t)/T_n$, is negligible. ΔR would represent the head-velocity signal from a canal pair and, if it were measured in deg/s, G would be the gain of the VOR or ~ 1.0 . During a lesion ΔR represents an equivalent imbalance between the bilateral VN that would generate nystagmus if the integrator were normal. Figure 12 illustrates how an imbalance nystagmus (Fig. 12A) coupled with a leaky integrator (Fig. 12B) can create nystagmus with curved slow phases (Fig. 12C) but, when T_n is small enough, fails to create nys-

tagmus and creates a null point instead. This was the usual pattern during the lesions and subsequent recovery.

At the null, eye velocity is zero so that, from Eq. 2

$$E(t) = G\Delta R T_n = E_{null}. \quad (3)$$

Since one could measure T_n and E_{null} , one could assess the imbalance ΔR except that it is unlikely that G would stay constant during a lesion. Nevertheless, it provides a qualitative picture of the state of imbalance. During the height of the lesion's effects, T_n was so close to zero that even a large imbalance would not only fail to generate nystagmus but would also not even appear as a large shift is null. As reported, between the first and second injections of a pair, the null shifted ipsilaterally by 10–20°. T_n , however, had already dropped to ~ 2 s and continued to drop to 0.6 s (Fig. 5, B and C) so that the imbalance, ΔR , was already being masked by this 10- to 30-fold drop in T_n . During recovery, the null was seen to deviate as far as 20–30° from center. At this time T_n was recovering toward 10 s and this probably allowed imbalances in the recovery process to be seen more clearly. Nevertheless, the lesions in all these experiments only led to a shift in the null point but never to spontaneous nystagmus. Why, after a unilateral lesion, the null point shifted ipsilaterally cannot even be guessed without knowing what the neurotoxins do to the discharge rates of type I and II cells in their vicinity.

VESTIBULOOCULAR REFLEX. An abnormally leaky integrator creates a complication for quantitatively analyzing vestibular nystagmus. As described in Eq. 2, the eye velocity may be viewed as a combination of the head velocity command (ΔR represents head velocity) and a drift caused by the integrator, $E(t)/T_n$. Because the drift velocity depends on eye position, every quick phase causes a sudden jump in the drift velocity that is superimposed on that of the slow phases. Unless one determines T_n , say from postsaccadic drift in the dark and corrects the measured eye velocity signal, for example by adding $E(t)/T_n$ to the sampled eye velocity record via a computer, it is virtually impossible to separate the drift and the head velocity contributions during VOR testing. Carpenter (6) was able to avoid this complication in the analysis of the VOR in cerebellectomized cats because he also performed de-

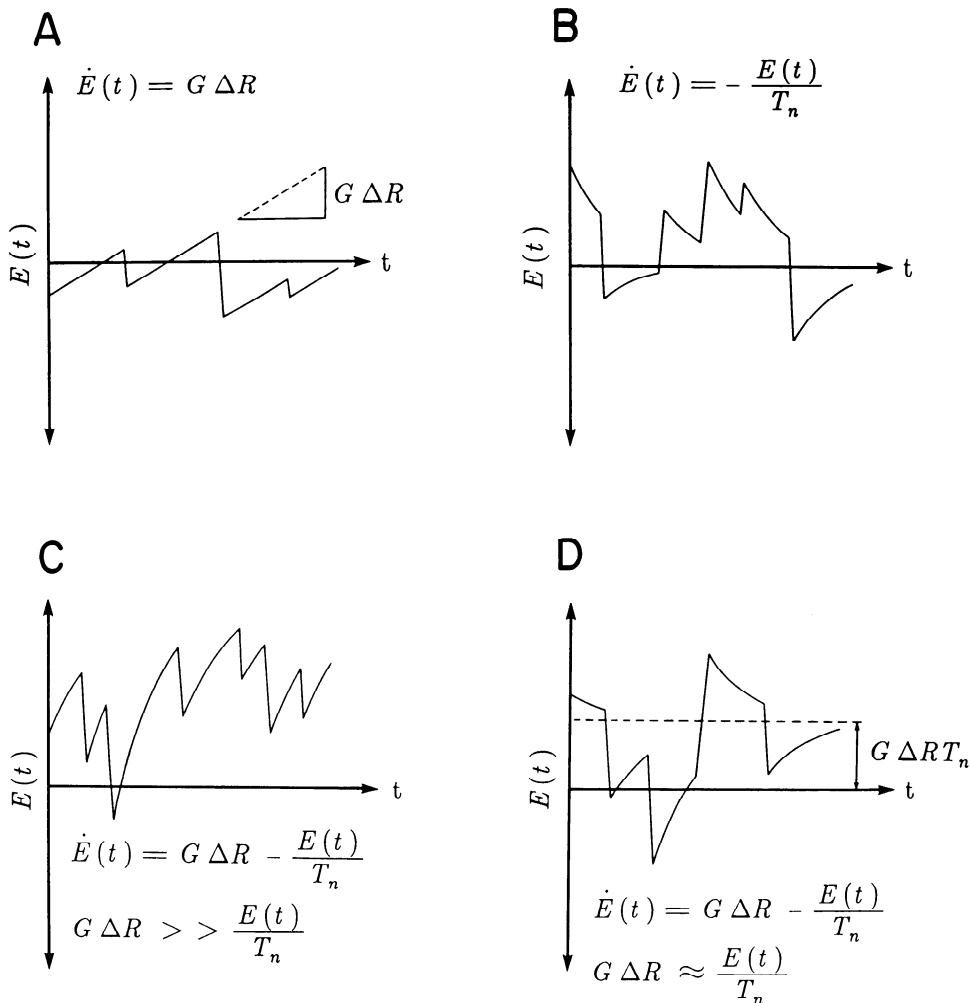


FIG. 12. Schematic forms of nystagmus caused by various combinations of push-pull firing rate difference and integrator leak. *A*: vestibular nystagmus due to a push-pull imbalance; note linear slow phases. *B*: gaze-evoked nystagmus caused by a leaky integrator. *C*: a combination of the two showing curved slow phases. Here the push-pull imbalance outweighs the leakiness of the integrator. *D*: gaze-evoked nystagmus with a push-pull difference and an integrator leak of similar degree of severity. This results in an offset null position. Eye position, \$E(t)\$; eye velocity, \$\dot{E}(t)\$; push-pull difference (spikes/s), \$\Delta R\$; gain in deg/s per spike/s, \$G\$; integrator time constant, \$T_n\$.

cerebration that interfered with the generation of quick phases. In two subsequent studies Godaux and Laune (18) and Cheron and colleagues (8) measured gain ratios and phase shifts from sinusoidal VOR testing as indicators of integrator function after administering a neuroleptic drug or making electrolytic lesions in the NPH and MVN of the cat. Although the Bode plots of the measured gain decrease and phase advance with decreasing frequency resemble the effect predicted from integrator impairment in a model for the VOR

in the absence of quick phases, in both studies the cats still generated quick phases, which complicates the eye movements and makes their measures quantitatively incorrect. Even though gain and phase were determined from eye-position records, as opposed to an eye-velocity signal, the problem of an eye-position dependent drift in the presence of quick phases still appears. For this reason we avoided sinusoidal stimuli; in the time domain, the difference between integrator drift and the result of a stimulus are easy to see, especially when

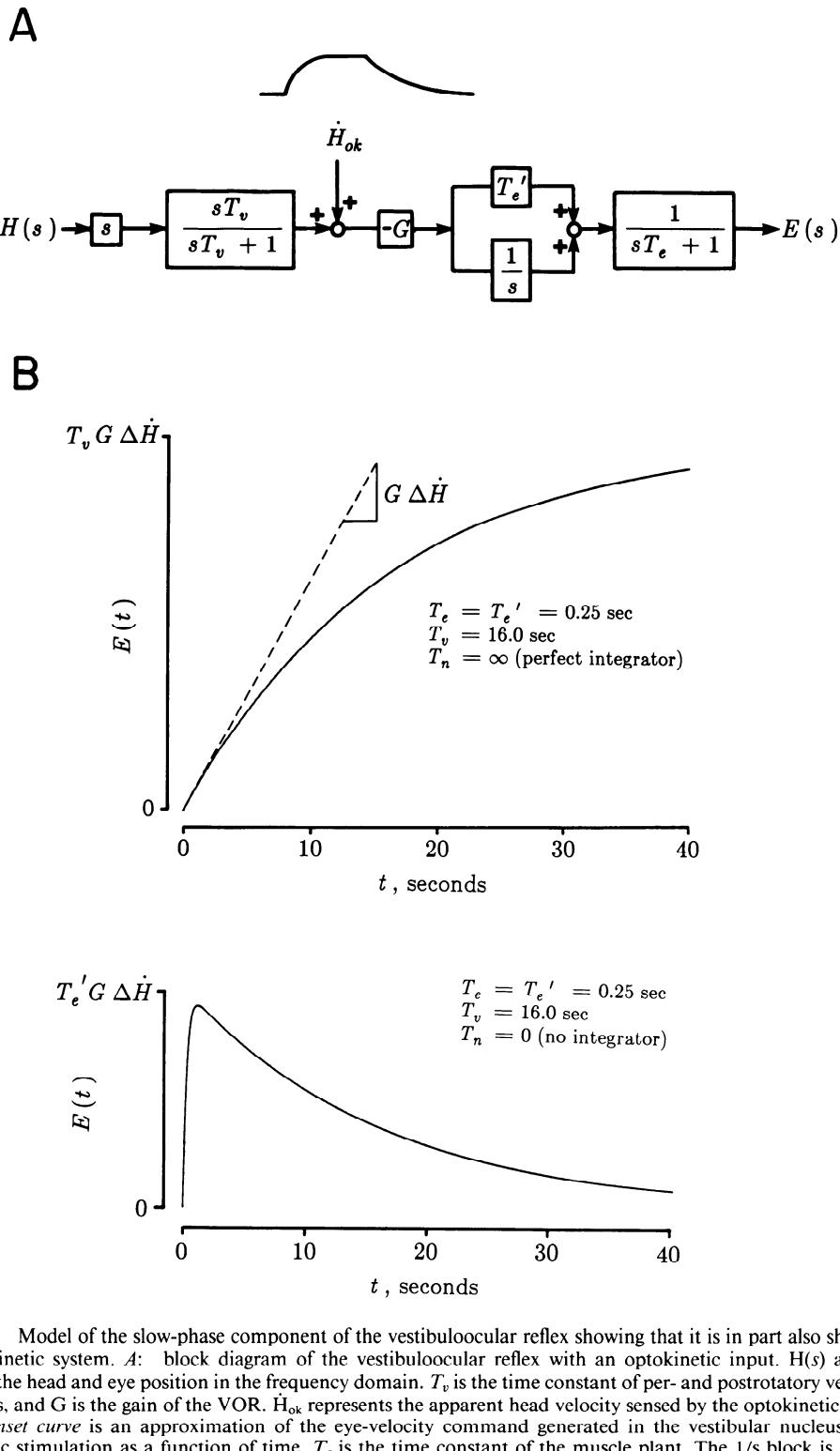


FIG. 13. Model of the slow-phase component of the vestibuloocular reflex showing that it is in part also shared by the optokinetic system. *A*: block diagram of the vestibuloocular reflex with an optokinetic input. $H(s)$ and $E(s)$ represent the head and eye position in the frequency domain. T_v is the time constant of per- and postrotatory vestibular nystagmus, and G is the gain of the VOR. \dot{H}_{ok} represents the apparent head velocity sensed by the optokinetic system, and the inset curve is an approximation of the eye-velocity command generated in the vestibular nucleus during optokinetic stimulation as a function of time. T_e is the time constant of the muscle plant. The $1/s$ block is an ideal

the integrator is very leaky (e.g., Figs. 7, 8, 10, and 11) and can be evaluated separately.

To verify that the time course in Fig. 7B is what one would predict in the absence of a neural integrator, the system shown in Fig. 1 was extended to that in Fig. 13A and analyzed. The high-pass element with a time constant T_v represents the combined effects of the canal dynamics and vestibular velocity storage. The muscle plant is approximated by a first-order lag with a time constant T_e . For simplicity, two extreme cases will be considered: a perfect neural integrator with no leak and a totally absent integrator. The Laplace transform description of the eye position is written for each case in Eqs. 4a and 4b. For a perfect neural integrator

$$\begin{aligned} E(s) &= -sH(s) \frac{sT_v}{sT_v + 1} G \left(T'_e + \frac{1}{s} \right) \frac{1}{sT_e + 1} \\ &= -\frac{sGT_v}{(sT_v + 1)} H(s) \end{aligned} \quad (4a)$$

since normally T'_e equals T_e . For an absent neural integrator

$$\begin{aligned} E(s) &= -sH(s) \frac{sT_v}{sT_v + 1} G \frac{T'_e}{sT_e + 1} \\ &= -\frac{s^2 GT'_e T_v}{(sT_v + 1)(sT_e + 1)} H(s). \end{aligned} \quad (4b)$$

For a constant-velocity step of head rotation, $H(s)$ equals $\Delta\dot{H}/s^2$ where $\Delta\dot{H}$ is the amplitude of the head velocity. Substituting this in Eq. 4a and solving for $E(t)$ yields, for the perfect integrator

$$E(t) = -G\Delta\dot{H}T_v(1 - e^{-t/T_v}) \quad (5a)$$

This is shown in the upper part of Fig. 13B. It is, initially, a ramp movement or the slow phase of nystagmus. Normally it would be interrupted by a quick phase in a second or less so only the initial part is relevant. If the integrator were absent from Eq. 4b

$$E(t) = -\frac{T_v T'_e G \Delta\dot{H}}{T_v - T_e} (e^{-t/T_v} - e^{-t/T_e})$$

or since T_e is much smaller than T_v

$$E(t) \approx -T'_e G \Delta\dot{H} (e^{-t/T_v} - e^{-t/T_e}) \quad (5b)$$

This curve appears at the bottom of Fig. 13B. After an initial rise governed by the time constant, T_e , eye position slowly falls back to zero with the time constant, T_v , similar to the tracing in Fig. 7B. There is no ramp or slow phases. From Eq. 5a, the eye velocity with an intact integrator is

$$\dot{E}(t) = -G\Delta\dot{H}e^{-t/T_v} \quad (6)$$

which is the same, except for the scaling factor, T'_e , as the eye-position response in the absence of the neural integrator for t greater than T_e (Eq. 5b). Of course the present model does not incorporate quick phases and so it does not apply during the rapid drifts after each quick phase in Fig. 7B. Unlike sinusoidal VOR testing, however, when steps of head velocity are used, one can easily distinguish in the eye position record between the drifts associated with each quick phase and the intervening VOR response. Thus, after a lesion in the region of the MVN and NPH, the position response to a step of head rotation had the same shape as the predicted response for the case of no neural integrator.

Part of the difficulty in quantifying the gain of the VOR acutely after a lesion is provided by Eq. 5b. Since T_v is greater than T_e (typically 6–16 vs. 0.2 s), the initial peak change in eye position, $T'_e G \Delta\dot{H}$, might be used as a measure of VOR gain, G . However, T'_e is the gain of the feed-forward pathway of the eye-velocity signal. Since this value would be expected to change under lesion conditions, trying to determine G by this method would not work. Although the amplitude of the initial step change in eye position did increase with larger head velocities, measuring the net gain, $G T'_e$, would have little interpretive value.

The results shown in Fig. 9 indicate that vestibular velocity storage was also impaired. With respect to Fig. 13A, this effect is lumped in the parameter T_v , which represents the cascade combination of cupula dynamics and velocity storage. Acutely after a lesion, T_v decreased to approximately the time constant of the cupula, ~ 6 s. Since single-unit recording has demonstrated that the increase in T_v above that of the cupula is already present on second-

neural integrator in parallel with a feedforward gain, T'_e , normally equal to T_e . B: the transient response of the eye position as a function of time for a step head velocity equal to $\Delta\dot{H}$. The upper half shows the response with an ideal neural integrator, whereas the lower half is the predicted response in the absence of a neural integrator.

order vestibular neurons (3), it is not surprising that vestibular velocity storage was affected by the injections in the region of the VN. Waespe et al. (39) have demonstrated that the nodulus and uvula also participate in vestibular velocity storage. These regions form reciprocal connections with the VN, and this network may effect velocity storage for vestibular signals.

A rather surprising finding was the preservation of the quick-phase triggering mechanism in the absence of normal slow phases. Figure 7B shows that even when the integrator was severely damaged so that there could be no slow phases generated, quick phases were nevertheless made in the direction of head turning. This was also the case during optokinetic stimulation (Fig. 8B). The intriguing aspect of this is that most models assume that quick phases are triggered when the difference between some internal variable or "center of interest" and eye position reaches a threshold. In the absence of slow phases the threshold would never be reached and no quick phases would be generated by such models. The present findings imply that either the stochastic nature of the internal variable is sufficient to sporadically trigger quick phases or there must be some other underlying trigger mechanism.

OPTOKINETIC RESPONSE. The effects of lesions in the region of the MVN and NPH on the optokinetic response shown in Fig. 8 can also be analyzed by the model of Fig. 13A. The optokinetic signal, \dot{H}_{ok} , present in the VN during stimulation is known to rise in a few seconds to a steady-state level (41). The initial jump in eye velocity is believed to be due to the pursuit system, considered below, with different pathways to the neural integrator. The nomenclature, \dot{H}_{ok} , reflects the observation (*ibid*) that this signal represents the estimate by the optokinetic system of the velocity of the head with respect to the visual environment, in this case the drum. When the lights are extinguished, \dot{H}_{ok} decreases to zero exponentially with the time constant of optokinetic velocity storage. Without the neural integrator this signal or eye-velocity command would produce a change in eye position of $GT'_e \bar{D}$ where \bar{D} is drum speed. Unlike the transient canal signal, the constant retinal image slip during illumination caused a sustained eye deviation. When the light was extinguished, the decay in optokinetic velocity storage de-

termined the rate at which the eye position decayed back to base line. Thus, similar to vestibular testing, in the absence of the neural integrator, the eye position response during optokinetic stimulation had the waveform that the eye-velocity tracing would normally have.

Cheron et al. (7) reported various optokinetic responses after electrolytic lesions in the region of the NPH and MVN. In some cases there was no coherent tracking of optokinetic stimuli, whereas in others there was an attenuated response with a decrease in the steady-state optokinetic gain and abolition of optokinetic after-nystagmus. No instances of a constant, deviation in eye position were observed during constant-velocity optokinetic stimulation. In this regard it should be noted that the cat has very poor pursuit. Consequently, they hypothesized that in some animals the optokinetic input to the final common pathway was completely interrupted or that in animals with diminished responses the neural integrator was lesioned. Although the eye position tracing clearly demonstrated integrator failure on the basis of postsaccadic drift, none of their aberrant optokinetic responses provided direct evidence of an isolated integrator defect.

Figure 9 shows that the time constant for per- and postrotatory vestibular nystagmus recovered more or less simultaneously with the time constant of optokinetic after-nystagmus. This result supports the general belief that a common velocity storage element is shared by both of these oculomotor systems (29, 32).

PURSUIT. If one accepts the proposition that the initial step increase in slow-phase velocity that occurs at the onset of illumination for constant-velocity optokinetic stimulation is mediated by the pursuit system (33, 45), then Figs. 8 and 10 support the hypothesis that the lesions also eliminated the integrator for pursuit eye movements. Instead of creating a ramp eye movement the pursuit velocity command was relayed directly to the motoneurons and caused a step change in eye position. After several hours of recovery, the animals did attempt to track small visual targets, and the conventionally accepted pursuit system could be tested directly. Figure 11 shows that while attempting to track a triangular waveform, catch-up saccades were required as the eyes moved eccentrically and, conversely, back-up

saccades were made to track the target centripetally. If $G\Delta R$ in Eq. 2 is viewed as the pursuit velocity signal, then both types of corrective saccades would be expected if the integrator were damaged; that is, if T_n were abnormally small in Eq. 2. As the eyes tracked eccentrically, the drift velocity contributed from the integrator leak, $E(t)/T_n$, subtracted from the pursuit velocity and catch-up saccades had to be made to stay on target. During centripetal tracking the drift and pursuit velocities added so that back-up corrective saccades were required. Thus with either full-field or small target stimuli, pursuit eye movements were also abnormal in the same manner that would be expected from a lesion of the neural integrator.

Relation of neural-network models of the integrator to the lesion data

We recently proposed a model of the neural integrator (4, 5) using lateral inhibition; each cell inhibited its neighbors and is inhibited by them in turn forming a positive feedback loop that perseverates activity—integration. It solved two major problems inherent in other models; it distinguished between background rates and the modulations on them (signals), integrating only the latter, and it was robust in that its behavior did not depend critically on any one connection. If, of course, a large fraction of synaptic connections are systematically altered, as a neurotoxin would undoubtedly do, it would cease to integrate entirely. The model is, at least, not incompatible with anatomical connections in the region of the brain stem lesions that affected the integrator. It contains three basic elements: 1) there must be inhibitory neurons, 2) the input must be driven in push-pull, 3) neurons receiving push and pull commands must mutually inhibit each other. The bilateral VN and NPH possess all three traits. Through major commissural projections, excitatory type I cells inhibit type I cells in the contralateral VN via an intervening type II inhibitory cell. This pathway could form the basis of the lateral-inhibitory connections in the model, which is equivalent to the commissural positive feedback network proposed by Galiana and Outerbridge (16). For the vestibular, optokinetic, and saccadic systems there is definitive evidence of a push-pull input. Clearly the primary vestibular afferents modulate in push-pull in

their projections to the VN. Single-unit recordings by Waespe and Henn (41) have shown that optokinetic signals are present on type I and II cells of the VN and so also participate via a push-pull action. Finally, excitatory and inhibitory burst cells project to the VN and NPH thereby providing a push-pull signal.

The reciprocal connections between the VN-NPH complex and the vestibulocerebellum raises the possibility that this latter structure may adaptively regulate the time constant of the neural integrator. Similar to a proposal by Galiana and Outerbridge (16), this could be achieved by regulating the gain of the commissural projections; that is to say, with respect to the model, shaping the profile of the inhibitory connections. This hypothesis could provide an explanation for the more moderate impairment of integrator function after cerebellectomy, and in particular flocculectomy.

After the majority of the initial injections, the integrator was severely damaged on the basis of postsaccadic drift in darkness. Although the possibility of diffusion of neurotoxin across the midline can not be absolutely excluded, enough of the lesion sites were far enough from the midline (>3 mm) that it is reasonable to propose that the lesion was initially unilateral. Evidently, both left and right halves of the network must be intact suggesting that the operation of the entire population is intimately linked via the commissural connections. Unlike previous notions of two complete half integrators on either side of the brain stem working in push-pull (44), the lesion data support the hypothesis of a single integrator perhaps built, in part, from commissural connections (16). A unilateral lesion never caused unilateral, gaze-evoked nystagmus. Waespe et al. (40) reported that monkeys with unilateral flocculectomy had gaze-evoked nystagmus only when looking toward the side of the lesion. No eye movement records, however, were published so one cannot rule out the possibility that they were observing (bilateral) gaze-evoked nystagmus with a large contralateral offset in the null position as in an extreme case of Fig. 12D. In the proposed model, our observations suggest that the inhibitory neurons that receive the push signal (e.g., afferents from one canal) and those that receive the pull signal (from the opposite canal) are largely segregated into one or the other

side of the brain stem and for each cell, the "neighbors" that it inhibits lie in the contralateral half of the brain stem reached through commissural projections.

The only experimental discrepancy from this hypothesis arises from reports of the effects of midline transection. According to the hypothesis, if all the lateral-inhibitory commissural connections were severed, then integrator function should be completely disrupted. After midline lesions in the medulla of the cat, caudal to the level of the abducens nuclei, Cheron et al. (8) did not observe postsaccadic drift. DeJong et al. (13) made larger midline sections that extended more rostrally in the monkey. Their eye movement records do show postlesion evidence of postsaccadic drift, but so do their prelesion records, as though the electro-oculogram had been amplified with AC coupling, despite claims to the contrary in their methods section, and this confounds the interpretation. Of course in both of these studies the possibility exists that there were intact commissural connections more ventrally or rostrally.

Clinical significance

Gaze-evoked nystagmus is regarded clinically as a rather nonspecific neurological finding. Such diverse insults as anticonvulsant therapy, sedation, cerebellopontine angle tumors and other structural lesions of the posterior fossa have been associated with gaze-evoked nystagmus. Discounting the effects of drugs, this clinical sign previously offered no more specific localizing value than a pathological process involving the posterior fossa,

in particular the vestibulocerebellum. The present results demonstrate that a lesion confined to the brain stem may produce intense gaze-evoked nystagmus. Thus it is no longer necessary to propose that a lesion arising in the brain stem, such as a glioma, has extended to the cerebellum or its peduncles on the basis of the presence of gaze-evoked nystagmus alone. On the other hand, discrete bilateral lesions in the region explored here are unlikely to be found clinically. One suspects that a small unilateral lesion might be compensated for, perhaps by the cerebellar connections, given one side intact. If so a bilateral lesion would be required for chronic signs. Unfortunately this region of the brain stem is so vital for other systems more essential to life that it would be rare for a patient to survive a bilateral lesion that included this region. Nevertheless, knowing the location of the neural integrator cannot help but influence in a basic manner, the way we examine and think about oculomotor disorders.

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