scales of several minutes or longer and thus might participate in such processes as habituation, sensitization, and long-term memory.

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References and Notes

1. T. H. Bullock, *Annu. Rev. Neuroscience* **5**, 121 (1982); A. E. Fessard, Ed., *Handbook of Sensory Physiology*, section 3, *Electroreceptors and Other Specialized Receptors in Lower Vertebrates* (Springer-Verlag, Berlin, 1974); A. J. Kalmijn, *Science* **218**, 916 (1982); R. D. Fields and G. D. Lange, *ibid.* **207**, 547 (1980); R. D. Fields, thesis, San Jose State University (1982).
2. B. Waltman, *Acta Physiol. Scand. Suppl. 264*, **66**; T. Szabo, *J. Microsc. (Paris)* **14**, 343 (1972); R. W. Murray, *J. Exp. Biol.* **39**, 119 (1962); G. N. Andrianov, H. R. Brown, O. B. Ilyinsky, *J. Comp. Physiol.* **93**, 287 (1974); M. V. L. Bennett, in *Fish Physiology*, W. S. Hoar and D. J. Randall Eds. (Academic Press, New York, 1971), vol. 5, pp. 443–574.
3. A. J. Kalmijn, *IEEE Trans. Magn.* **17**, 1113 (1981); *J. Exp. Biol.* **55**, 371 (1971); G. W. Heyer, M. C. Fields, R. D. Fields, A. J. Kalmijn, *Biol. Bull.* **161**, 344 (1981).
4. W. T. Clusin and M. V. L. Bennett, *J. Gen. Physiol.* **73**, 685 (1979); *ibid.*, p. 703; *ibid.* **69**, 121 (1977); *ibid.*, p. 145.
5. Bipolar silver hook or suction electrodes connected to a high-impedance A-C–coupled preamplifier were used to monitor responses from axons of the afferent neurons. The temperature was held near 10°C with a solid-state cooling device, and oxygen was bubbled into the well containing the sensory epithelium.
6. These changes were not significantly associated with postmortem time, recording time, the animal, the date of the experiment, or minor differences in the size organs (analysis of variance).
7. Tissue was fixed in the recording chamber, placed in cold fixative for several hours, and fixed again with 1 percent osmium tetroxide. The recording chamber was thoroughly washed, soaked in 5 percent lysine to quench reactivity of any remaining aldehydes, and rinsed in distilled water and buffer before reuse.
8. After secondary fixation for 1 hour in buffered 1 percent osmium tetroxide, tissue was washed in cacodylate buffer (*p*H 7.3), dehydrated in a graded series of ethanol and acetone, and embedded in epoxy resin. Sections were stained with uranyl acetate and lead citrate. Fixative contained 2 percent paraformaldehyde and 2.5 percent glutaraldehyde in 0.15*M* cacodylate buffer (*p*H 7.3), with 4 percent sucrose; osmolality = 1150 mOsm. Ringer solution contained the following: NaCl, 300 m*M*; $CaCl_2$, 2 m*M*; KCl, 4 m*M*; $MgCl_2$, 2 m*M*; $NaCHO_3$, 2.5 m*M*; urea, 315 m*M*; trimethylamine oxide (Sigma), 76 m*M*; Hepes buffer, 7.5 m*M* (*p*H 7.3); and glucose, 5 m*M*.
9. Ribbon synapses also occur in the retina [F. S. Sjostrand, *J. Ultrastruct. Res.* **2**, 22 (1958); J. E. Dowling, *Proc. R. Soc. (London) Ser. B.* **170**, 205 (1968)], the pineal body [J. A. McNulty, *Cell Tissue Res.* **215**, 491 (1981)], and electroreceptors of teleosts [A. W. Wachtel and R. B. Szamier, *J. Morphol.* **119**, 51 (1966)].
10. T. J. Sejnowski and M. L. Yodlowski, *J. Neurocytol.* **11**, 897 (1982).
11. Multiple sections of the same organ in different planes, and serial sectioning and reconstruction show that the synaptic morphology is bilaterally symmetrical, and the differences in morphology are not an artifact of the orientation or location of sectioning.
12. Mean squares of the depth of synaptic troughs among groups (organs of different thresholds) = 2527 nm (d.f. = 3), $P < 0.01$; among subgroups (among sense organs) = 400.8 (d.f. = 26), $P << 0.001$; within subgroups (within sense organs) = 59.5 (d.f. = 232). The mean depths of synaptic troughs were 429, 272, 265, and 238 nm for groups of organs classed according to thresholds of 0.001 to 0.01, 0.01 to 0.1, 0.1 to 1, and >1 μA.
13. The depth of the synaptic trough did not differ significantly among organs that were declining in sensitivity, increasing in sensitivity, or showed no change in sensitivity in the period prior to fixation (Bonferroni *t*-test for multiple comparisons).
14. J. E. Heuser and T. S. Reese, *J. Cell Biol.* **57**, 315 (1973); T. M. Miller and J. E. Heuser, *ibid.* **98**, 685 (1984); S. F. Schaeffer and E. Raviola, *ibid.* **79**, 802 (1978); M. Israel, Y. Dunant, R. Manaranche, *Prog. Neurobiol.* **13**, 237 (1979).
15. T. H. Bullock and P. J. Diecke, *J. Physiol. (London)* **134**, 47 (1956).
16. A. Sand, *Proc. R. Soc. (London) Ser. B* **125**, 524 (1938); R. W. Murray, in *Handbook of Sensory Physiology*, section 3, *Electroreceptors and Other Specialized Receptors in Lower Vertebrates*, A. Fessard, Ed. (Springer-Verlag, Berlin, 1974), pp. 125–146; T. H. Bullock, *ibid.*, pp. 1–12; W. R. Lowenstein, *Nature (London)* **188**, 1034 (1960); H. R. Brown and O. B. Ilyinsky, *J. Comp. Physiol.* **126**, 333 (1978).
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Dynamic Modification of the Vestibulo-Ocular Reflex by the Nodulus and Uvula

Abstract. *The time constant of the decay of slow-phase eye velocity of postrotatory nystagmus or optokinetic after-nystagmus is reduced during exposure to a stationary visual surround (visual suppression). It is also reduced after tilting the head (tilt suppression). A "dump" mechanism in the vestibulo-ocular reflex has been proposed to rapidly discharge activity from the central vestibular system during both types of suppression. Monkeys lost this mechanism after lesions of the nodulus and uvula. They also lost the ability to habituate the time constant of nystagmus on repeated exposure to optokinetic and vestibular stimuli. Periodic alternating nystagmus, which is believed to represent an instability in the vestibulo-ocular reflex, was observed in two of three monkeys. These data indicate that the nodulus and uvula play an important role in suppressing, habituating, and stabilizing the vestibulo-ocular reflex.*

Rotation of the head causes activation of the vestibulo-ocular reflex (VOR), producing compensatory eye movements that maintain gaze. If the visual surround moves with the head, signals from the VOR responsible for compensatory eye movement must be suppressed if images are to remain stable on the retina. The visual system accomplishes this by several processes. One, involving the flocculus, directly opposes activity from the VOR (*1*). This mechanism is responsible for the rapid rise in slow-phase velocity during optokinetic nystagmus (OKN) (*2*) and is utilized in mediating ocular pursuit (*1, 3*). Another process shortens the dominant time constant of the VOR by quickly discharging or "dumping" activity stored in the vestibular system, thereby reducing residual eye velocity (*4*). Specific brain structures that are associated with the dumping process have not been identified.

Eye velocity can be suppressed during nystagmus in other ways that do not involve the visual system. If the head is tilted during postrotatory nystagmus, eye velocity decays rapidly to zero (*5, 6*). Since tilting probably does not modify the time constant of activity coming from the semicircular canals, the shortened time constant is not likely to be due to a change in the peripheral signal that drives the system. Instead there must have been a discharge or "dump" of activity stored in the VOR (*4*). Consistent with this is a rapid decay in slow phase eye velocity of optokinetic after-nystagmus (OKAN) after tilting (*6, 7*). We have proposed that the same dump mechanism that rapidly alters the time constant of the VOR during visual suppression (*2, 4*) is used by the vestibular system to discharge stored activity in response to head tilt (*6*). We now provide evidence in support of this idea and show that the dynamic modification of the VOR time constant is mediated through the nodulus and uvula of the vestibulocerebellum.

Eye movements of three rhesus monkeys (*Macaca mulatta*) and one nemestrina monkey (*M. nemestrina*) were recorded with electrooculography (EOG). Animals were tested in a three-axis vestibular and optokinetic stimulator to establish baseline values for horizontal and vertical per- and postrotatory nystagmus, OKN, and OKAN (*2, 4, 6, 8*). The nodulus and uvula were removed by suction-ablation under anesthesia. Animals were tested for periods of 2 to 3 months, and the extent of lesions was determined in three animals after their deaths. In each monkey the nodulus and ventral uvula were destroyed. The fastigial nucleus was invaded on the left side in one animal, but the other roof nuclei were intact.

OKN, OKAN, and per- and postrota-

tory nystagmus, induced by steps of angular velocity about a vertical axis, were normal in each of the animals before the lesions were made. Time constants of vestibular nystagmus and OKAN, originally as long as 20 to 30 seconds in each of the monkeys, fell to 8 to 12 seconds when they were tested repeatedly (Fig. 1A). Each animal exhibited the dumping phenomenon. That is, exposure to a stationary visual surround during postrotatory nystagmus (visual suppression) (t_0 in Fig. 1C) caused an immediate decline in slow-phase velocity as well as a loss of stored activity from the central vestibular system over a period of 5 to 10 seconds. The loss of stored activity in Fig. 1C is demonstrated by the failure of the velocity of postrotatory nystagmus to recover when the animal was put back into darkness at t_1. The dotted line, taken from Fig. 1A, shows the expected decline in slow-phase velocity, had the animal been in darkness during the postrotatory nystagmus. The time constant of the decline in stored activity in light was about 3 to 5 seconds, similar to the time constant of decay seen previously (*4*). Visual suppression had a similar effect on OKAN. That is, OKAN was suppressed in light and, depending on the period of exposure to the stationary surround, was reduced or did not reappear when the animals were put back into darkness. From 6 to 10 seconds of exposure to a stationary surround were adequate to completely discharge stored activity during OKAN.

Tilting the normal animal during postrotatory nystagmus in darkness (Fig. 1B) also caused a decrease in the decay time constant of slow-phase velocity. The time constant of postrotatory nystagmus after tilting (Fig. 1B) can be compared with that recorded with the animal upright during the postrotatory period (Fig. 1A). In contrast to visual suppression, there was no immediate rapid fall in slow-phase eye velocity at the onset of tilt (t_0). Rather, eye velocity decayed smoothly to zero after a latency of about 1 second. The nature of the decay suggests that it could be modeled simply by modifying the time constant of the velocity storage integrator. A similar change in time constant has been used as part of visual suppression in previous models (*2, 4*). In support of a common mechanism being utilized during both visual suppression and tilt suppression, the time course of the smooth decay of slow-phase velocity was similar for both responses (Fig. 1, B and C). Consistent with the proposed loss of stored activity in central structures, there was no return of slow-phase velocity when the animal was moved back to the upright position (t_1 in Fig. 1B).

After nodulectomy and partial uvulectomy, the gain of the VOR was unchanged. The time constant of postrotatory nystagmus increased to about 30 seconds (Fig. 1D). This was the dominant time constant of the VOR that had been present when testing had first begun. (Note the difference in time base between Fig. 1, A to C, and Fig. 1, D to F.) The time constant of OKAN was similarly increased after nodulectomy to about 30 seconds in two of the four animals (Fig. 2C). After the lesions, repeated exposure to rotatory or optokinetic stimuli no longer caused shortening of the time constant of either postrotatory nystagmus or OKAN. Thus the ability to habituate the time constant of per- and postrotatory nystagmus and OKAN was lost after removal of the nodulus and uvula. These effects, which have been described before (*9*), were permanent and did not recover.

After surgery exposure to a stationary visual surround during postrotatory nystagmus (t_0 in Fig. 1F) caused the same initial rapid drop in slow-phase eye velocity as before the lesion (Fig. 1C). However, eye velocity did not decay rapidly to zero after the initial drop, but stayed at approximately the same level throughout the period of exposure to the stationary visual surround. When the lights were extinguished (t_1), slow-phase eye velocity recovered to a value close to that which would have been expected had there been no period of suppression

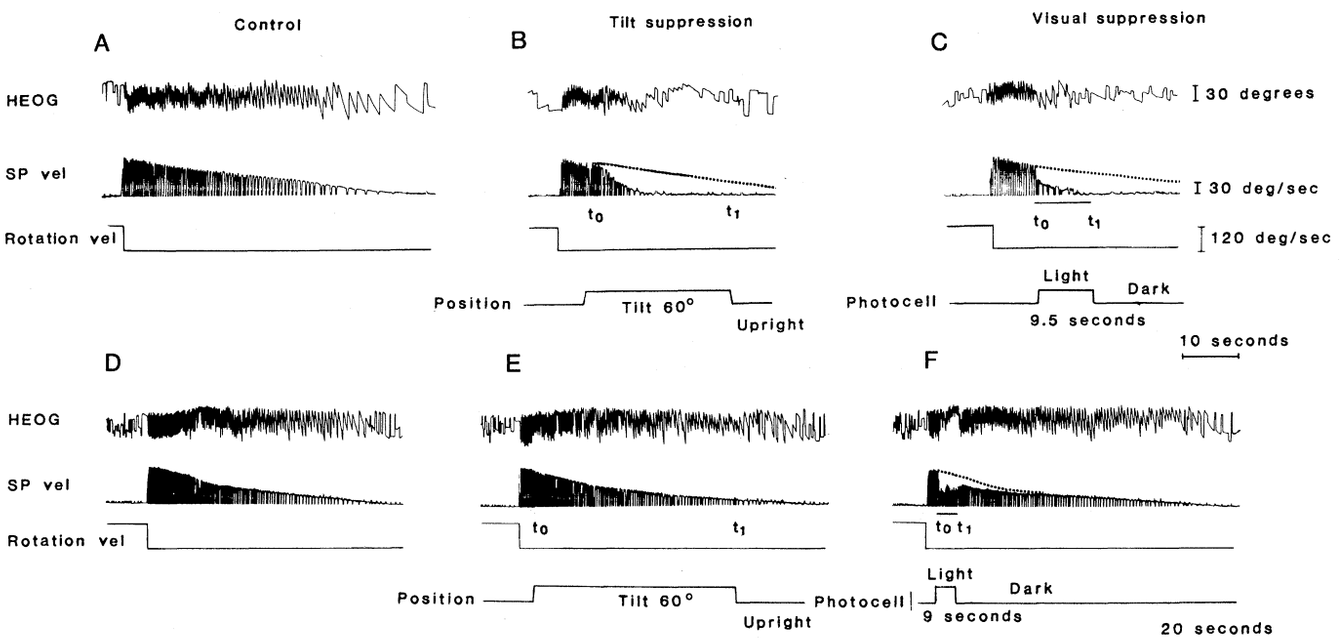

Fig. 1. Horizontal postrotatory nystagmus induced by angular rotation at a constant velocity of 120 deg/sec, before (A to C) and after (D to F) nodulo-uvulectomy. Eye velocities associated with saccades have been manually removed for clarity. In (B) and (E), the monkey was tilted 60° to the right at the upward deflection of the chair position trace (t_0) and brought back to the upright at the downward deflection (t_1). In (C) and (F), the animal was exposed to a stationary lighted surround at t_0 for the period shown by the solid bar under the slow-phase velocity trace. The lights were turned off at t_1. The dotted lines in (B), (C), (E) and (F) show the expected decline in slow-phase velocity if the animal had been upright and in darkness during the postrotatory period, extrapolated from the slow-phase velocity envelope of (A). The time base for (A to C) is shown under (C) and that for (D to F) under (F). Abbreviations: HEOG, horizontal EOG; SP, slow phase; vel, velocity.

(dotted line in Fig. 1F). The nystagmus then declined over a time course similar to that of postrotatory nystagmus in darkness (Figs. 1F and 1D). Only after a period of suppression of 20 to 30 seconds did the nystagmus not reappear when the animal was put back into darkness. The time constant of the decline in stored activity when the animal was continuously exposed to a stationary visual surround was 8 to 12 seconds, whereas it had been 3 to 5 seconds before surgery.

Results were similar during OKAN. A period of visual suppression that had completely dumped stored activity before the lesion (6 seconds) caused only a slight decrease in the velocity of nystagmus when the animal was once again in darkness (t_1 in Fig. 2A). Eye velocity did not recover to the level that would have been present had there been no period of suppression (dashed line in Fig. 2A). This indicates that the visual system had not entirely lost its ability to decrease the time constant of decay of stored central activity during suppression. This capability was markedly attenuated, however.

Effects of removing the nodulus and uvula on tilt-suppression of nystagmus were equally striking. After surgery, tilting the animals had no effect on the time constant of vestibular postrotatory nystagmus (t_0 and t_1 in Fig. 1E), and time constants during trials when the animals were tilted were the same as when the animals were upright (Fig. 1D). Results were similar during OKAN (Fig. 2C). This indicates that tilt suppression of nystagmus was lost after nodulectomy and partial uvulectomy.

The initial fast rise in slow-phase velocity at the onset of OKN was unaffected by the lesions. This is consistent with the hypothesis that the rapid rise in OKN slow-phase velocity is mediated by the flocculus (*10, 11*); the nodulus and uvula are probably not involved in this function.

In addition, two of three monkeys that were tested for it had periodic alternating nystagmus after the nodulus and ventral uvula had been removed. The response occurred within several minutes after animals were put into darkness and was not present in light. The time to onset was shorter when the monkeys had received preceding optokinetic or vestibular stimulation. An example of nystagmus alternating after an optokinetic stimulus of 60 deg/sec is shown in Fig. 2, A and B. The primary phase of OKAN was followed by a brisk secondary phase (Fig. 2A), which was then succeeded by continuous alternations in the direction of the nystagmus (Fig. 2B). Peak velocities of the alternating nystagmus were 25 to 35 deg/sec, and occurred at periods of 180 to 300 seconds. Periodic alternating

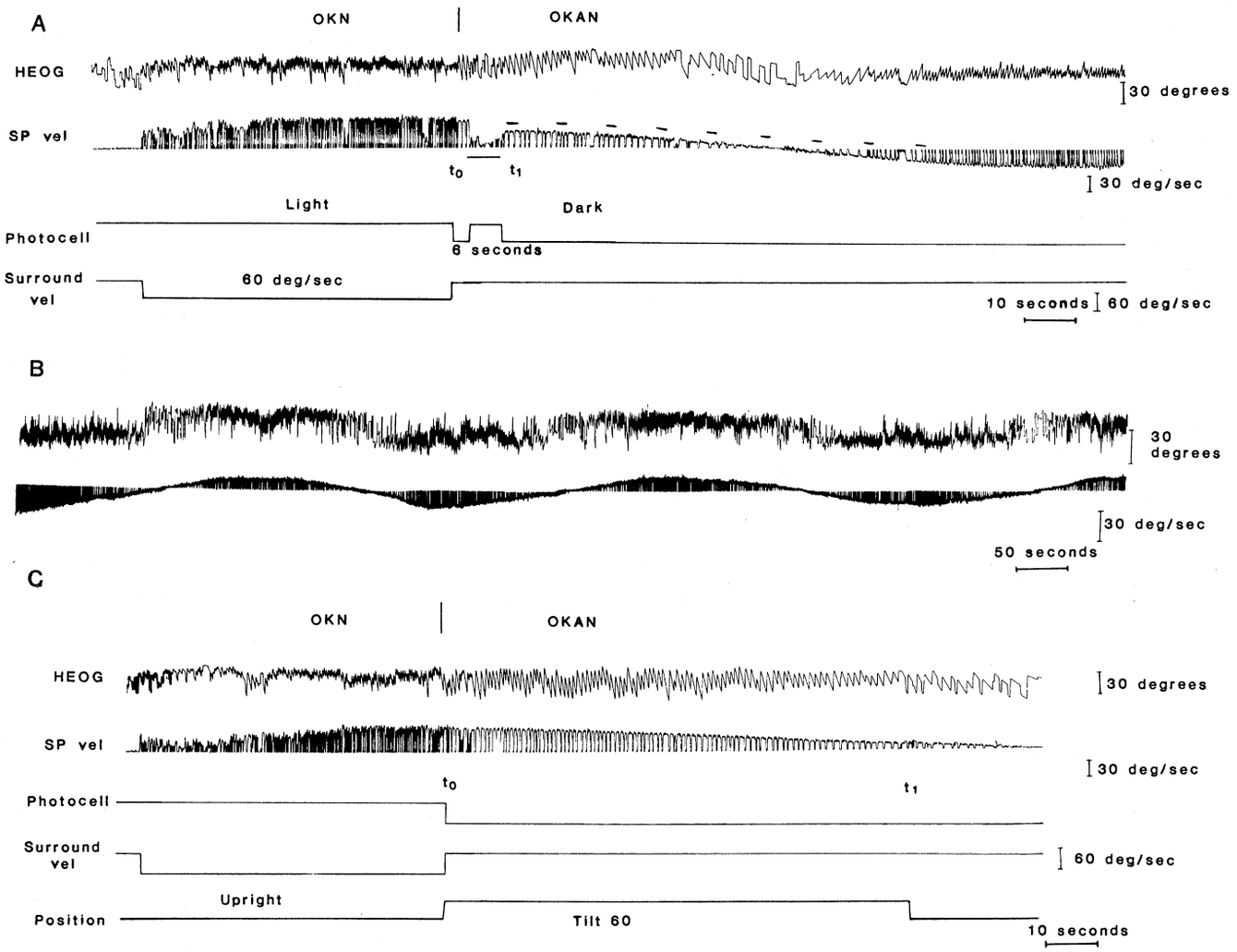

Fig. 2. OKN, OKAN, and periodic alternating nystagmus induced by movement of the visual surround at 60 deg/sec after nodulectomy. Eye velocities associated with saccades have been manually removed for clarity. In (A) the lights were turned on for a 6-second period during OKAN at t_0. This resulted in a reduction in slow phase velocity which partially recovered when darkness was restored at t_1. The dashed line shows the velocity during primary OKAN that would have been expected had there been no period of suppression. (B) Continuation of (A), but at 1/5 the speed. Nystagmus continued to wax and wane as long as the animal was in darkness. (C) The animal was tilted 60° from the upright at t_0. At t_1 it was brought back to the upright position.

nystagmus in some humans is effectively reduced with baclofen (30 mg/day) (*12*). The alternating nystagmus was abolished in both monkeys at dosages of less than 10 mg/day.

These data are consistent with the idea that there is a mechanism that can dynamically shorten the dominant time constant of the VOR in response to certain types of visual and vestibular stimulation. These include conflicting visual and vestibular stimuli or head position changes during postrotatory nystagmus or OKAN. This mechanism seems to depend on the integrity of the nodulus and uvula, as it is lost when they are removed. Whereas a single process could be responsible for the rapid discharge of activity during tilt suppression, several processes probably cause the changes in eye velocity during visual suppression. One is associated with pathways through the flocculus that directly oppose signals arising in the vestibular system to null compensatory eye movements (*1, 3, 10, 11*). It has no effect in discharging stored activity responsible for slow-phase velocity in the vestibular nuclei (*13*). Another dynamically sluggish process, using pathways from the accessory optic system and pretectum (*14*), is responsible for charging and discharging activity in the central vestibular system (*4, 11, 15*). Because it stores activity related to slow-phase velocity, it has been called a "velocity storage" mechanism (*2, 4*). Presumably, the small loss in slow-phase velocity during attempts at visual suppression during postrotatory nystagmus (Fig. 1F) or OKAN (Fig. 2A) was due to activation of this mechanism by a central representation of retinal slip. Acting on the velocity storage mechanism is the "dump" mechanism that is lost after nodulus and uvula lesions. Although it rapidly discharges residual stored activity, it does not charge the velocity storage integrator.

On the basis of these results, we propose that the flocculus and the nodulus and uvula have complementary roles in modifying the vestibulo-ocular reflex. The flocculus mediates rapid changes in eye velocity from the visual system. It aids the VOR in stabilizing gaze during ocular compensation and suppresses the VOR when watching targets or a visual surround that moves with the head. The nodulus and uvula, on the other hand, appear to have little or no effect on visual and vestibular pathways that cause rapid changes in eye velocity. Instead they affect the VOR by dynamically controlling the dominant time constant of the velocity storage integrator. This could be accomplished through their direct connections to the vestibular nuclei (*16, 17*). Differences in function between the flocculus and the nodulus and uvula may be related to the differential projections of these areas (*16*).

The nodulus and uvula may also have more global functions in controlling the VOR. It was not possible to habituate the time constant of either per- or postrotatory nystagmus or OKAN after nodulo-uvulectomy, and previous modifications of the VOR time constant were lost. There was also periodic alternating nystagmus in two of three animals after operation. Such nystagmus has been modeled as the oscillation of an unstable nonlinear system (*18*). Thus, the nodulus and uvula may also be important in habituating and stabilizing the vestibulo-ocular reflex (*19*).

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References and Notes

1. S. G. Lisberger and A. F. Fuchs, *J. Neurophysiol.* **41**, 764 (1978).
2. B. Cohen, V. Matsuo, T. Raphan, *J. Physiol. (London)* **270**, 321 (1977).
3. F. A. Miles and J. H. Fuller, *Science* **189**, 1000 (1975).
4. T. Raphan, V. Matsuo, B. Cohen, *Exp. Brain Res.* **35**, 229 (1979).
5. F. Guedry, *Acta Otolaryngol. (Stockholm)* **60**, 30 (1965); A. J. Benson and M. A. Bodin, *Aerospace Med.* **37**, 144 (1966).
6. T. Raphan, B. Cohen, V. Henn, *Ann N.Y. Acad. Sci.* **374**, 44 (1981).
7. OKAN is due to activity produced in the central vestibular system by movement of the visual surround. Peripheral afferent activity from the semicircular canals is unchanged during OKN or OKAN. [U. Buettner and W. Waespe, *Exp. Brain Res.* **41**, 310 (1981)].
8. V. Matsuo and B. Cohen, *ibid.* **53**, 197 (1984).
9. W. Halstead, G. Yacorzynski, F. Fearing, *Am. J. Physiol.* **120**, 350 (1937); G. T. Singleton, *Laryngoscope* **77**, 1579 (1967).
10. D. Zee, A. Yamazaki, P. H. Butler, G. Gucer, *J. Neurophysiol.* **46**, 878 (1981).
11. W. Waespe, B. Cohen, T. Raphan, *Exp. Brain Res.* **50**, 9 (1983).
12. G. M. Halmagyi, P. Rudge, M. A. Gretsy, R. J. Leigh, D. S. Zee, *Ann. Neurol.* **8**, 609 (1980).
13. W. Waespe and B. Cohen, *Exp. Brain Res.* **51**, 23 (1983).
14. W. Precht and P. Strata, *Neuroscience* **5**, 777 (1980).
15. W. Waespe and V. Henn, *Exp. Brain Res.* **27**, 323 (1977).
16. P. Angaut and A. Brodal, *Arch. Ital. Biol.* **105**, 441 (1967).
17. W. Precht, R. Volkind, M. Maeda, M. L. Giretti, *Neuroscience* **1**, 301 (1976).
18. R. J. Leigh, D. A. Robinson, D. S. Zee, *Ann. N.Y. Acad. Sci.* **374**, 619 (1981).
19. Supported by PHS grants NS-00294 and EY-04148, Core Center grant EY-01867, Swiss National Foundation grant 3.718-0.80, and a grant from the Young Men's Philanthropic League. We thank D. Helwig, V. Rodriguez, and D. Borras for assistance.
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Digestive Adaptations for Fueling the Cost of Endothermy

Abstract. *Little is known about the digestive adaptations that enable mammals to sustain metabolic rates an order of magnitude higher than those of reptiles. Comparison of several features of digestion in mammals and lizards of similar size eating the same diet revealed that mammals processed food ten times faster and with the same or greater extraction efficiency. Transport kinetics and rates of nutrient absorption normalized to the quantity of intestinal tissue were similar in these two classes of vertebrates. The main basis for faster absorption in mammals is their much greater intestinal surface area.*

The differences in respiratory, circulatory, reproductive, and excretory physiology between mammals and reptiles have been much studied. However, little is known about the differences in digestive physiology that fuel the metabolic cost of endothermy. Mammals have metabolic rates and hence food requirements exceeding those of lizards by an order of magnitude (*1*), and there are at least eight types of digestive adaptations that could in theory enable mammals to meet this greater need for nutrients: faster food processing; higher extraction efficiency at the same body temperature; higher efficiency due to higher body temperature at night; greater intestinal surface area at the macroscopic, microscopic, or submicroscopic levels; and higher nutrient transport rates due to higher passive permeability or to higher capacities or binding affinities of active transport mechanisms. Although transit times (*2, 3*), extraction efficiencies (*3, 4*), and rates of transport (*5–7*) have been measured in some species of mammals and lizards, these quantities depend on diet and body size (*5–8*), and comparisons between mammals and lizards of the same size eating the same diet are lacking. The mechanisms underlying measured extraction efficiencies and transport rates in lizards remain unexplored.

Thus, quantitative assessment of the various factors that might account for the high digestive rates of mammals is