effective. The intracellular concentration of sodium may be estimated from the equilibrium potential as about 9 mmole/liter. From the measurements of the peak currents (80 ma/cm$^2$) the influx of sodium during a single spike is of the order of 0.01 mmole/liter. These calculations indicate that eel electroplaques may possess a very active "pump" mechanism for extruding sodium.

Despite the absence of an active repolarizing process the duration of the spike of eel electroplaques is only 2 to 3 msec (*7*). However, the time constant of the cell membrane is only about 75 $\mu$sec, as was also confirmed in the present work. Thus, passive decay of the membrane potential from the peak voltage of the spike should be rapid. Even if, due to potassium inactivation, the time constant increases three- or fourfold, the potential should decay to negligible values in about 1 msec after depolarizing electrogenesis is terminated by sodium inactivation. This is confirmed by the voltage-clamp data, since the phase of inward current lasted only 1 msec or less (Fig. 1).

An earlier finding on eel electroplaques (*7*), which seemed to be anomalous in the light of data on other cells, is accounted for by the coupled occurrence of potassium inactivation and the absence of potassium activation. When neural stimuli generate depolarizing postsynaptic potentials during the falling phase of a directly elicited spike the two depolarizations sum. The summation results because the falling phase of the spike represents a passive decay of the membrane potential.

Depolarizing inactivation has been observed in crayfish (*10*) as well as frog (*11*) skeletal muscle fibers and in cardiac muscle (*12*). It has been analyzed with voltage clamp techniques in electroplaques of several species of the weakly electric Gymnotid relatives of the electric eel (*13*) and in supramedullary neurons of the puffer (*14*). Eel electroplaques, to our knowledge, present the first example in which the depolarization of the electrically excitable spike-generating membrane does not cause the repolarizing electrogenesis and delayed rectification which are attributable to potassium activation.

YUTAKA NAKAMURA
SHIGEHIRO NAKAJIMA
HARRY GRUNDFEST

*Laboratory of Neurophysiology,*
*Department of Neurology,*
*College of Physicians and Surgeons,*
*Columbia University, New York 10032*

**References and Notes**

1. A. L. Hodgkin and A. F. Huxley, *J. Physiol.* **117**, 500 (1952).
2. K. S. Cole and H. J. Curtis, *J. Gen. Physiol.* **22**, 649 (1939).
3. M. Altamirano, *J. Cell. Comp. Physiol.* **46**, 249 (1955); ——— and C. W. Coates, *ibid.* **49**, 69 (1957).
4. H. Grundfest, *Progr. Biophys. Biophys. Chem.* **7**, 1 (1957); *Biol. Bull.* **119**, 288 (1960).
5. H. Grundfest, *Ann. N.Y. Acad. Sci.* **94**, 405 (1961); ———, in *Properties of Membranes and Diseases of the Nervous System* (Springer, New York, 1962); ———, in *The General Physiology of Cell Specialization* (McGraw-Hill, New York, 1963).
6. J. W. Moore and K. S. Cole, in *Physical Techniques in Biological Research*, vol. 6, pt. B, *Electrophysiological Methods*, W. L. Nastuk, Ed. (Academic Press, New York, 1963).
7. R. D. Keynes and H. Martins-Ferreira, *J. Physiol.* **119**, 315 (1953); M. Altamirano, C. W. Coates, H. Grundfest, *J. Gen. Physiol.* **38**, 319 (1955).
8. T. Narahashi, T. Deguchi, N. Urukawa, Y. Ohkubo, *Am. J. Physiol.* **198**, 934 (1960); S. Nakajima, S. Iwasaki, K. Obata, *J. Gen. Physiol.* **46**, 97 (1962); T. Narahashi, J. W. Moore, W. R. Scott, *ibid.* **47**, 965 (1964); Y. Nakamura, S. Nakajima, H. Grundfest, *Biol. Bull.*, in press.
9. T. Furukawa, T. Sasaoka, Y. Hosoya, *Japan. J. Physiol.* **9**, 143 (1959); W. R. Loewenstein, C. A. Tersuolo, Y. Washizu, *Science* **142**, 1180 (1963); H. B. Higman and E. Bartels, *Biochim. Biophys. Acta* **54**, 543 (1962).
10. J. P. Reuben and H. Gainer, *Nature* **193**, 142 (1962).
11. S. Nakajima, S. Iwasaki, K. Obata, *J. Gen. Physiol.* **46**, 97 (1962); T. Szaimi, T. Tomita, *Japan. J. Physiol.* **13**, 641 (1963).
12. A. E. Hall, O. F. Hutter, D. Noble, *J. Physiol.* **166**, 225 (1963).
13. M. V. L. Bennett and H. Grundfest, *Federation Proc.* **21**, 357 (1962); ———, *Proc. 22nd Congr. Intern. Union Physiol. Sci.* (Excerpta Medica Foundation, Amsterdam, 1962), vol. 2, abstr. 783.
14. S. Nakajima and K. Kusano, *Abstracts of 7th Annual Meeting Biophysical Society, New York (1963).*
15. This work was supported in part by grants from the Muscular Dystrophy Associations of America; research grants NB-03728-02 and NB-03270-03 from the U.S. Public Health Service and training grant 5-TI-NB-5328-02; and grant G 19969 from the National Science Foundation. Y. Nakamura is a trainee fellow, U.S. Public Health Service; S. Nakajima was a fellow of the United Cerebral Palsy Research Foundation.

10 August 1964

## Activating and Synchronizing Centers in Cat Brain: Electroencephalograms after Lesions

Abstract. *Electroencephalographic changes occur after small unilateral lesions have been made in the pontine tegmentum of cats with permanently implanted electrodes. Lesions in the area of the nucleus reticularis pontis oralis produce electroencephalographic synchronization (sleep pattern). Lesions in the pontine and caudal midbrain tegmentum, dorsal, lateral, and caudal to the lesions producing synchronization, produced electroencephalographic activation (waking pattern).*

The states of sleep and wakefulness in adult animals are generally expressed in the electroencephalogram (EEG) by synchronization (high-voltage, slow waves) and activation (low-voltage, fast waves), respectively (*1*). An exception is the activated EEG of paradoxical sleep. Within the limits of the pons there are structures that produce synchronization or activation when destroyed (*2*). We have sought to determine more precisely the location and limits of these structures.

We used 30 cats under general anesthesia. Silver-ball electrodes were implanted on the dura of both sides of the brain over the motor, auditory, and visual cortex to record electrical activity and stereotactically oriented steel electrodes were implanted to produce diathermocoagulation. Ten days later EEG control records were obtained from the free unanesthetized animals in an electrically shielded box. Since synchronization and activation periods vary considerably in adult cats, the control records were of long duration. The records, taken periodically for a month after the localized lesions had been made, were of the same duration as the control records and were made under the same conditions.

Quantitative analysis of synchronization and activation periods in the records of animals with lesions, relative to the amount of synchronization and activation found in control records, allowed us to differentiate between the lesions that produce synchronization and those that produce activation. The unilateral lesions in the pontine tegmentum were 2 to 3 mm in diameter. Figure 1 (*A*, *C*, *D*, and *E*) shows the combined areas where lesions gave rise to the two types of EEG activity.

The degree of activation in the control records (before the lesions were made) in all the animals of each group was considered to be zero (Fig. 1*B*). The absolute values of zero were different for the two groups of animals. The curves represent the percentage of activation (positive values) or synchronization (negative values) as deviations from the control level of activation.

Lesions in the reticular formation of the pons (nucleus reticularis pontis ora-

lis and nucleus reticularis ventralis), rostral to the main sensory nucleus of the trigeminus, produced an increase in synchronization during the month after the lesion was made. These were central lesions in the reticular formation of the pons which in no case extended mesially to the midline or laterally to the nuclei of the lateral lemniscus. Their caudal margin was approximately that of the posterior tip of the nucleus reticularis ventralis but was rostral to the anterior pole of the oliva superior.

The lesions that gave rise to an increase in EEG activation during the month after the destruction were for the most part in the pons at the level of the nucleus reticularis pontis caudalis, caudal to, but slightly overlapping the areas where lesions produced synchronization. Some were dorsal to the synchronizing areas, including lesions situated in the caudal midbrain tegmentum as well as lesions that completely destroyed the tractus brachium conjunctivum. Others were lesions situated laterally to the synchronizing lesions, that is, lesions in the lateral lemniscus and in the nuclei of the lateral lemniscus, including the brachium pontis. The lesions of the tractus brachium conjunctivum give rise to certain characteristic waves in the contralateral frontal cortex (*3*).

Figure 1*B* represents only the analyses of the EEG records from the cerebral hemisphere on the same side as the lesion. No ostensible difference was observed with respect to activation in the contralateral hemisphere. After the lesions that produced synchronization had been made, on the other hand, even though a bilateral synchronization existed, the effect was more marked on the side of the lesion.

These findings confirm that in the rostral part of the pons there are structures responsible for activation since their destruction gives rise to synchronization. We conclude that these structures are the nucleus reticularis pontis oralis and the nucleus reticularis ventralis, since synchronization was found only when the lesions destroyed a sufficient area of these nuclei. A few long, ascending connections originate in these nuclei and through them pass only a small part of the ascending fibers originating in more caudal regions.

Synchronizing influences from the nucleus reticularis pontis caudalis and its neighboring formations, together with the long ascending connections and the influences of special importance from the neo-cerebellum, project toward the center. The unilateral destruction of restricted parts of these nuclei and pathways gives rise to EEG activation.

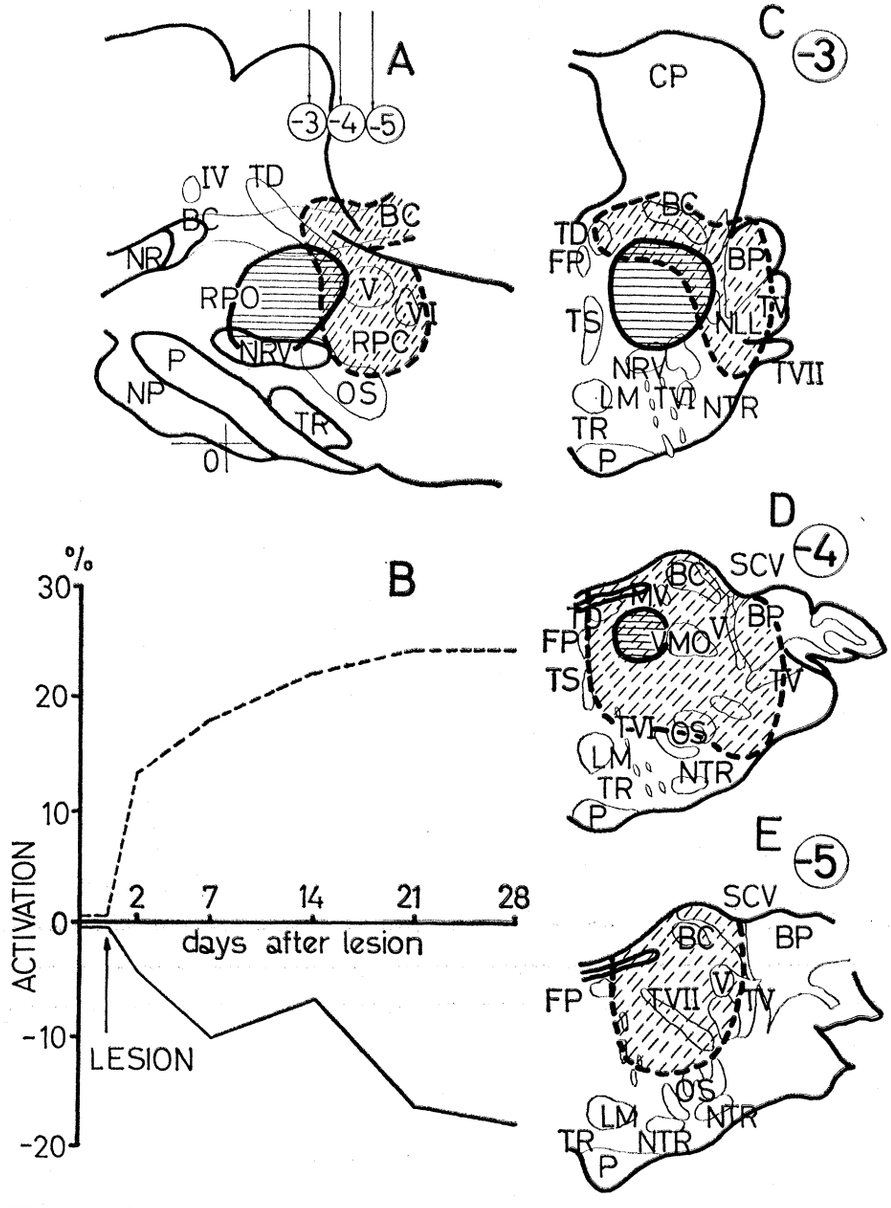


Fig. 1 (*A*, *C*, *D*, and *E*). Diagrams of the combined extent of lesions in the brain stem of cats which give rise to EEG activation (diagonal dashed lines encircled by heavy dashed lines) and synchronization (horizontal lines encircled by heavy solid lines). (*A*) Sagittal section 2 mm from midline. Structures in the plane of the section are indicated by heavy lines; those in other sagittal planes are shown by light lines. Circled numbers indicate Horsley-Clarke frontal plane levels of the Reinoso-Suárez atlas (*4*). (*B*) Graph showing the percent of increase in activation (lesions of the first type) or the percent of decrease in activation (lesions of the second type) relative to a control-based zero for each animal, as determined prior to lesion. (*C*, *D*, and *E*) Sections in the frontal plane indicated by circled numbers. Note that lesions which produced synchronization (horizontal lines) are situated at the level of the nucleus reticularis pontis oralis and the lesions which produced activation (diagonal lines) are situated dorsal, lateral and caudal to the others. *BC*, brachium conjunctivum; *BP*, brachium pontis; *CP*, colliculus inferior; *FP*, fasciculus longitudinalis medialis; *LM*, lemniscus medialis; *MV*, tractus mesencephalicus nervi trigemini; *NLL*, nucleus lemnisci lateralis; *NP*, nucleus pontis; *NR*, nucleus ruber; *NRV*, nucleus reticularis ventralis; *NTR*, nucleus corporis trapezoidei; *OS*, oliva superior; *P*, tractus pyramidalis; *RPC*, nucleus reticularis pontis caudalis; *RPO*, nucleus reticularis pontis oralis; *SCV*, tractus spinocerebellaris anterior; *TD*, nucleus tegmenti dorsalis; *TR*, corpus trapezoideum; and *TS*, tractus tectospinalis.

Therefore, the interference with an equilibrium which exists between afferent influences, some of which originate in the pons and some of which ascend through it, is an important factor in the maintenance of the waking state as indicated by the electroencephalogram.

The suppression of the synchronizing influences affects the cerebral hemispheres bilaterally, while the suppression of the activating influences affects mainly the hemisphere on the side of the lesion.

A. CAMACHO-EVANGELISTA
F. REINOSO-SUÁREZ
*Sección del C.S.I.C., Universidad de Navarra, Pamplona, Spain*

**References and Notes**

1. F. Bremer, *Compt. Rend. Soc. Biol.* **122**, 1235 (1935); G. Moruzzi and H. W. Magoun, *Electroencephalog. Clin. Neurophysiol.* **1**, 455 (1949).
2. J. P. Cordeau and M. Mancia, *Arch. Ital. Biol.* **96**, 374 (1958); C. Batini, G. Moruzzi, M. Palestini, G. F. Rossi, A. Zanchetti, *Arch. Ital. Biol.* **97**, 1 (1959); G. F. Rossi, K. Minobe, O. Candia, *Arch. Ital. Biol.* **101**, 470 (1963).
3. A. Camacho-Evangelista, *Ann. Anat. Pathol.* **9**, 429 (1962).
4. F. Reinoso-Suárez, *Topographischer Hirnatlas der Katze* (Merck, Darmstadt, 1961).
5. This work was supported in part by grants from the U.S. Public Health Service (B-3208 and NB-04312).

4 August 1964

## Auditory Nuclei: Distinctive Response Patterns to White Noise and Tones in Unanesthetized Cats

Abstract. *Electrical responses to "white" noise and tonal stimuli were recorded from unanesthetized cats with permanently implanted bipolar electrodes. The cochlear nucleus, inferior colliculus, and medial geniculate each showed distinctive patterns of evoked activity. White noise and tones produced qualitatively different types of response. A decrease in activity characterized the response of the inferior colliculus to tonal stimuli.*

Electrophysiological studies of the auditory pathway have been pursued in hopes of finding differences in "spontaneous" activity and in response characteristics that might underlie some functional localization. In the course of other experiments on the auditory nuclei functional differences were observed that were not anticipated from data reported in studies of single units (*1*, *2*). We found that white noise produced a marked increase in activity in the inferior colliculus, while pure tonal stimuli produced a marked decrease below the spontaneous level. In contrast, in the cochlear nucleus both white noise and tones evoked an increase in activity. This report describes subsequent verification of these observations carried out in a rigorously controlled acoustic environment.

Responses were recorded from five cats with bipolar electrodes chronically implanted in the dorsal and ventral cochlear nucleus, inferior colliculus, and medial geniculate body, pars principalis. All electrode placements were later verified histologically. Electrodes were made of 32- or 36-gauge enameled stainless steel wires with only the cut ends bared and separated by 1 to 2 mm. Muscles of the middle ear were left intact in all animals. The middle ears were examined post mortem and were found to be free from infection. Unanesthetized and unrestrained cats were placed in a wire mesh enclosure (45 by 60 by 45 cm) in the center of an Eckel anechoic chamber (free-field area, 114-cm cube). White noise (flat from 20 to 20,000 cy/sec ± 1 db) and tonal stimuli (from 100 cy/sec to 18,500 cy/sec) were presented through a Quad electrostatic speaker, mounted in the anechoic chamber 1 meter above the animal enclosure. Sound pressure level in the chamber was monitored continuously with a condenser microphone (*3*) (response flat from 20 to 20,000 cy/sec ± 2 db). Purity of the tonal stimuli and whiteness of the noise were checked with a sound and vibration analyzer (*3*). All sound pressure levels (SPL) were referred to 0.0002 dyne/cm$^2$. The background level of sound in the chamber was 52 db ± 4. Within the enclosure variation in SPL of white noise and tones of 85 db was less than ± 3 db. Responses at each electrode site to three or more presentations of each stimulus were studied on at least four separate days. Electrical activity was photographed on an oscilloscope and averaged with an "integrator" (*4*). Integration was obtained by passing the conventional a-c amplified recording through a full-wave rectifier and smoothing filter; the resulting d-c output was proportional to the amplitude and frequency of the conventional recording. The units of integration were $\mu$v-msec.

Figure 1 shows representative simultaneous recordings from the cochlear nucleus and inferior colliculus of an unanesthetized cat, at the onset and offset of white noise (80 db) and 2500-cy/sec tone (80 db). Sustained white noise produced a sustained increase in activity above the spontaneous level and termination of the noise was followed by a depression of spontaneous activity (*4*). The 2500-cy/sec tone produced the same effect as white noise in the cochlear nucleus, but in the inferior colliculus produced a marked decrease in activity below the spontaneous level. The termination of the tone was often followed by an overshoot above the spontaneous level in the inferior colliculus. Figure 2 shows the integrator record of the entire course of these events. Frequency analysis and oscilloscopic monitoring at fast sweep speed showed that the changes in amplitude of the recorded activity were due to changes in the number and/or frequency of individual neuronal discharges, not merely to changes in synchronization.

Recordings from all five electrodes implanted in the cochlear nucleus showed an increase in activity in response to tones between 300 and 3000 cy/sec. The largest responses were evoked by tones of 1000 to 2000 cy/sec. These responses were of greater amplitude than the response to white noise of the same intensity. Tones above 3000 cy/sec produced small decreases in activity at two of the electrodes in the cochlear nucleus and no response at the other three. Frequency-following (bursts of activity phase-locked to the stimulus cycle) was seen up to 4000 cy/sec.

Recordings from all seven electrodes implanted in the inferior colliculus showed decreased activity in response to tones above 2000 cy/sec. Recordings from three electrodes showed no increase for any tones and a marked decrease from 200 to 18,500 cy/sec. Recordings from the other four electrodes showed an increase in activity from 300 to 1500 cy/sec and a marked decrease for higher frequencies. These two patterns of response could not be related to the position of the electrode tips within the nucleus; for example, anterior as opposed to posterior, dorsal as opposed to ventral, or in proximity to incoming lemniscal fibers instead of in the main body of the nucleus. High amplitude frequency-following accompanied all increases in activity but was also occasionally observed at low amplitude in response to tones which produced a decrease in activity.

Recordings from the three electrodes implanted in the medial geniculate body showed a slight decrease in activity in