Anesthesiology
V 36, No 4, April 1972

The EEG, Evoked Potentials, and Single-unit Activity during Ketamine Anesthesia in Cats

Y. Kayama, M.D., and K. Iwama, M.D.†*

The effects of ketamine in cats which were allowed to move about freely or restrained only minimally were studied. EEG, evoked potentials, and single-unit activity were recorded. Soon after intravenous injection of ketamine, low-voltage fast waves of the sensorimotor and visual cortices increased in amplitude, and the on-going theta waves of the hippocampus were replaced by desynchronized activity. Later, the seizure activity in the neocortex, as well as that in the hippocampus, appeared as bursts. Ketamine markedly enhanced the evoked potentials of the sensorimotor and visual cortices in response to electrical stimulation of the medial lemniscus and optic chiasm, respectively. Ketamine-induced EEG desynchronization of the sensorimotor cortex was associated with an increase in spontaneous unitary discharges. These findings were interpreted as indicating that the effect of ketamine is to stimulate the neocortex, hippocampus, and other subcortical nuclei concurrently, eventually inducing seizure activity. This challenges the concept of ketamine as a dissociative anesthetic. (Key words: Ketamine; Transmission; Single-unit activity; Electroencephalogram.)

DOMINO and his associates were the first to study the mechanisms of action of ketamine in cats by recording spontaneous EEG patterns and evoked potentials, both cortical and subcortical.[1, 2] They found that ketamine induced hypersynchronous delta waves in the thalamo–neocortical system and theta-arousal waves in the hippocampus. They interpreted these findings as depression of the thalamo–neocortical system with activation of the limbic system and thus, as functional "dissociation." Accordingly, they proposed that ketamine was a dissociative anesthetic.[3–4]

Our experiment was designed to obtain more explicit information about the electrographic changes during ketamine anesthesia. Using cats moving about freely or with minimum restraint, we studied the effects of ketamine, iv, on spontaneous EEG patterns of the neocortex and hippocampus, cortical evoked potentials, and cortical single-unit activity. We found that the neocortex and the hippocampus were affected by ketamine in virtually the same way, challenging the concept of ketamine as a dissociative anesthetic.

Methods

Fifteen cats prepared for recording electrical activities of the neocortex and hippocampus were studied in 65 chronic experiments. Using pentobarbital anesthesia (35 mg/kg, intraperitoneally) each cat was fixed in a stereotaxic apparatus. Small stainless steel electrodes were screwed to the skull overlying the sensorimotor and visual cortices. A parallel bipolar needle electrode of insulated stainless steel was placed in the dorsal hippocampus at a depth which evoked high-amplitude seizure discharges. Bipolar electrodes of the same type were introduced into the medial lemniscus and optic chiasm. The position of the lemniscal electrode was determined by observing potentials evoked by single-shock stimulation of the skin of a paw. The chiasmal electrode was positioned using potentials evoked by flash stimulation of the eyes. All deep electrodes were fixed to the skull with dental cement.

Some cats were prepared for recordings of cortical-unit activity. By trephination, a small hole was made in the skull over the sensorimotor cortex or around a point of the lateral

* Visiting Researcher. On leave from the Department of Anesthesiology, Yamaguchi Universiyt Medical School, Ube, Yamaguchi, Japan.
† Professor of Neurophysiology.
Received from the Department of Neurophysiology, Osaka University Medical School, Kita-ku, Osaka, Japan. Accepted for publication October 22, 1971.
Address reprint orders to Dr. Y. Kayama, Department of Anesthesiology, Yamaguchi University Medical School, Ube, Yamaguchi, Japan.

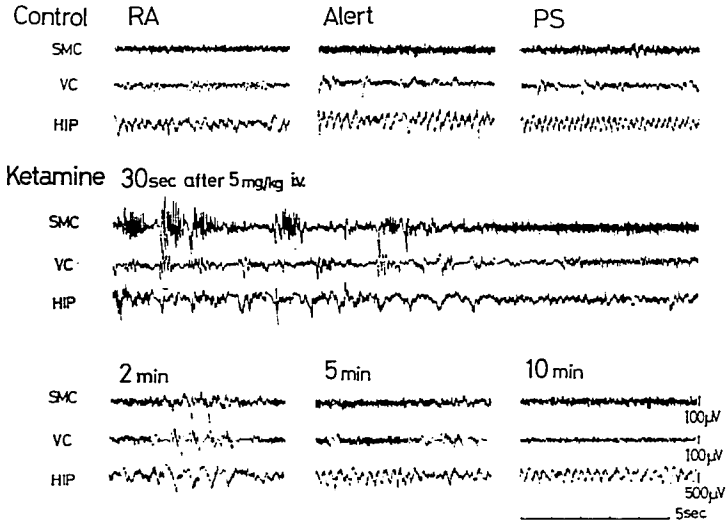

FIG. 1. Effects of intravenously-administered ketamine on the electroencephalographic pattern of an unrestrained cat. SMC, sensorimotor cortex; VC, visual cortex; Hip, hippocampus. *Top,* records made during arousal at rest (RA), alertness (Alert) and paradoxical sleep (PS). *Center,* from 30 to 50 sec after ketamine, 5 mg/kg, was injected. The cat was asleep (slow-wave sleep). Toward the right the EEG's were all desynchronized. *Bottom,* records made 2, 5, and 10 min after injection. EEG seizures are evident at 2 min. The VC record at 5 min still shows EEG seizures.

gyrus at AP 0 to −3 mm. Concentrically with this hole a metallic tube (diameter 8 mm, height 10 mm) was fixed to the skull. The dura was left intact. To make possible unitary recording with painless fixation of the head, the method of Noda *et al.*[5] was followed: a mound of dental cement was made on the skull and two aluminum tubes (diameter 8 mm, length 35 mm) were embedded in it horizontally and parallel, with a separation of about 4 cm. Pressing two pairs of ear bars against the aluminum tubes sufficed to fix the head to a stereotaxic apparatus.

To administer ketamine intravenously, a polyethylene tube (diameter 1 mm, length 15 cm) was inserted into a subcutaneous vein of the foreleg or neck and led to the head underneath the skin. A syringe needle containing heparin was connected to the end of the tube and fixed to the skull with dental cement.

After allowing at least two days for recovery, studies of the effects of ketamine were begun. For studies of EEG patterns and evoked potentials the cat was placed in a box (40 × 40 × 60 cm) with an observation window. It was allowed to move about freely. For stimulation of the medial lemniscus and optic chiasm electrical pulses 0.05 msec in duration were applied at various intensities. EEG's and evoked potentials were led to R-C amplifiers (RB-2, Nihonkohden) and then to an oscilloscope (VC-7, Nihonkohden) in conjunction with a pen-recorder (WI-260, Nihonkohden). EEG's were recorded on paper. Evoked potentials, displayed on the oscilloscope screen by a rapid sweep, were photographed.

In studies of single-unit activity the cat's

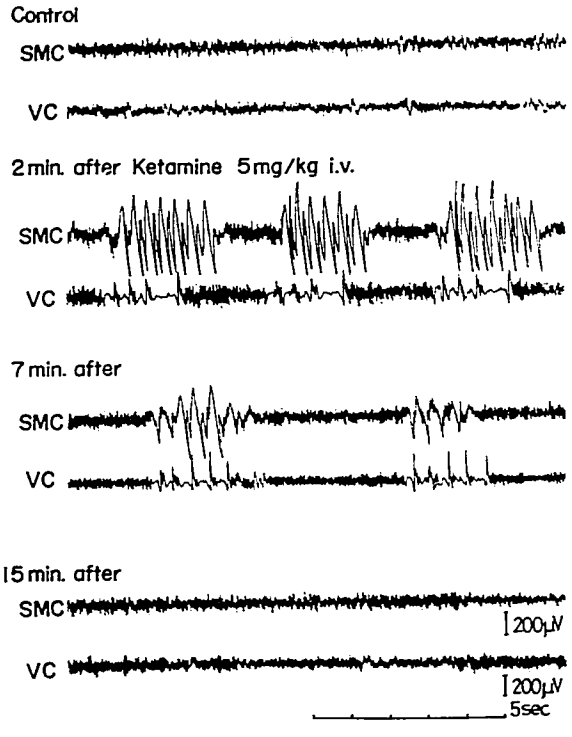

FIG. 2. Ketamine-induced EEG seizures. Two minutes after ketamine was injected, enhanced fast waves of the sensorimotor (SMC) and visual cortices (VC) were interrupted by bursts of seizure activity. The seizures were spike-and-wave complexes in the SMC and spiky waves in the VC (*second row*). Later, the seizures gradually subsided (*third row*), and finally they disappeared (*fourth row*).

head was fixed to a stereotaxic apparatus as described and the body was placed horizontally on a board. Microelectrodes, made of stainless steel and insulated with Insl-X, were inserted into the cortex through the metallic tube placed concentrically with the trephined hole. Movement of the cortex was minimized by filling the inside of the metallic tube with agar. Unitary spikes were led to a cathode follower, displayed on an oscilloscope, and recorded on film. In addition, amplified spikes were led to a Schmitt circuit and converted into 3-msec rectangular pulses. This made it possible to record unitary spikes on paper simultaneously with the EEG's.

For stimulation of visual cortical units a shadow of the experimenter's hand was moved on a dimly illuminated screen placed in front of the cat's eyes. Touch, pressure, and electrical stimuli were applied to the skin to activate sensorimotor cortical units.

The doses of ketamine administered intravenously ranged from 3 to 5 mg/kg in the EEG and evoked-potential studies. The dose was 2 mg/kg in most of the unitary activity studies. The drug was injected as a single dose given within 30–60 seconds. When the same cat was studied on more than one occasion, at least a day was allowed between experiments for recovery. In studies of cortical

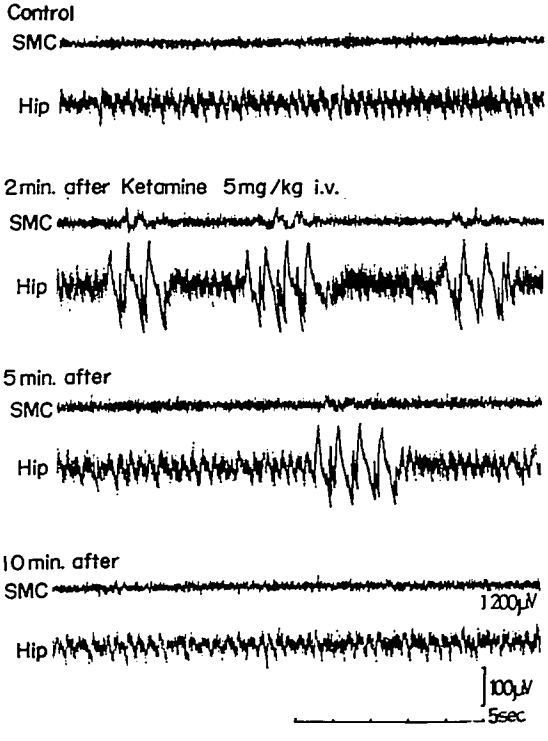

FIG. 3. Ketamine-induced EEG seizures in the sensorimotor cortex (SMC) and hippocampus (Hip). They are evident as spike-and-wave complexes in the hippocampus and slow waves in sensorimotor cortex.

unitary activity ketamine was injected at intervals of about an hour, and in most animals the total doses remained below 10 mg/kg.

Results

BEHAVIOR AND THE EEG

Changes in behavior and EEG's were first noted about 30 sec after ketamine, 3–5 mg/kg. The eyes were fully open, with a fixed gaze, and the pupils were maximally dilated. The cat licked its lips and showed profuse salivation. The head remained elevated and was sometimes shaken slowly, but no overt movements of the body and extremities were observed. There were occasional twitching movements of vibrissae, ears, and some shoulder muscles. Often the cat extended its forelimbs and crouched flat on the floor. When the cat was forced to assume an abnormal posture, it easily fell onto its side. The cat paid no attention to visual, auditory, or painful stimuli, although it often spontaneously displayed a searching response similar to that elicited by activation of the limbic system.[6, 7] After a larger dose of ketamine (8–10 mg/kg), the cat strongly extended all four limbs, assuming a posture similar to opisthotonus. Recovery from ketamine, 3–5 mg/kg, took about 10 minutes after the injection. The cat

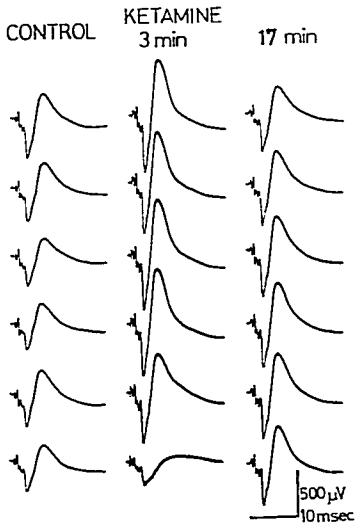

FIG. 4. Visual cortical evoked potentials before and after injection of ketamine, 5 mg/kg. Evoked potentials were produced by single-shock stimulation of the optic chiasm. Control records (*left*) were obtained during arousal at rest. Enhancement of the evoked potential was greatest 3 min after injection (*center*) and had decreased slightly at 17 min (*right*). Sweeps in each column were consecutive.

began to move but was severely ataxic. At this stage it reacted to strong painful stimuli, although the defensive responses were very poor. Ataxia persisted for 20–30 minutes; all effects of ketamine seemed to have disappeared after an hour. These behavioral changes agree well with those reported previously.[2]

EEG records from the sensorimotor and visual cortices and hippocampus before and after ketamine, 5 mg/kg, are shown in figure 1. The records made during arousal at rest (RA), alertness induced by the presence of a rat in the cat's view (Alert) and paradoxical sleep (PS) are in the top row; those made during slow-wave sleep are in the leftmost part of the center row. This cat's EEG patterns during these behavioral states were typical and were consistent with those described by previous investigators.[5, 9]

In this experiment ketamine (5 mg/kg) was injected during slow-wave sleep. About 40 seconds after the injection, the cat opened its eyes, lifted its head, and began to salivate. Concomitantly, the EEG's were all strongly desynchronized (rightmost part of records in center row). Then, on the background of enhanced low-voltage fast waves, groups of three to five slow waves appeared simultaneously in all of the EEG's. The slow waves gradually increased in amplitude to a maximum about 2 minutes after the injection (left records, bottom row). Sharp spikes were superimposed on the slow waves of the neocortical EEG's. The wave frequency in one burst of slow waves was about 1.5 Hz; the burst recurred at intervals of about 4 seconds. As time passed, ketamine-induced slow waves tended to disappear, leaving the desynchronized background activity almost unchanged. Five minutes after injection, the EEG's were similar to those seen in the state of alertness, although some slow waves with superimposed

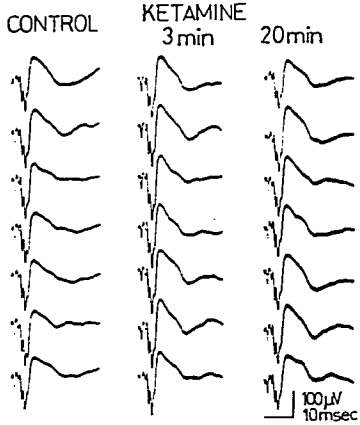

FIG. 5. Enhancement of sensorimotor cortical evoked potentials by ketamine. Single shocks were applied to the medial lemniscus. Control records were obtained during arousal at rest. Sweeps in each column were consecutive.

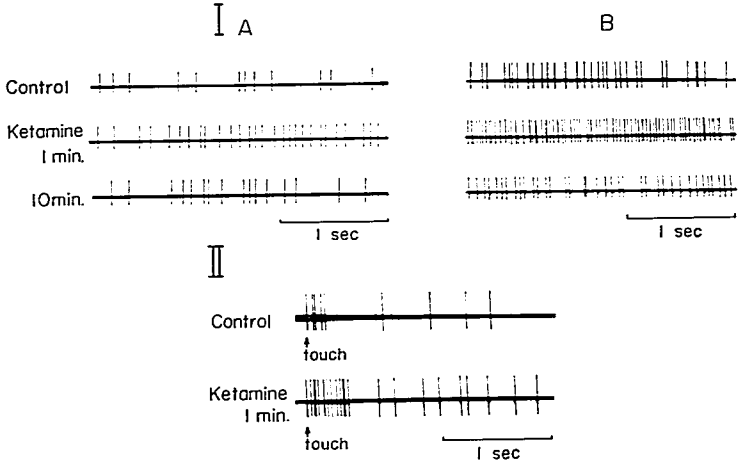

FIG. 6. Unitary activity of the sensorimotor cortex before and after injection of ketamine, 2 mg/kg. *I*, spontaneous discharges of two different units (*A* and *B*). Control records were obtained during arousal at rest. Discharge rates increased a minute after injection of ketamine and returned to the control level after 10 min. In every phase the discharge rates of unit *A* were slower than those of unit *B*. *II*, evoked discharges of another unit. The number of spikes occurring in response to tactile stimulation increased after injection of ketamine.

spikes remained in the visual cortex (center records, bottom row). The visual cortex finally ceased to show slow-wave activity about 10 minutes after the injection (right records, bottom row); EEG's remained in a pattern of alertness for more than an hour. In sum, ketamine enhanced low-voltage fast waves and then induced bursts of slow waves with or without superimposed spikes in the neocortical and hippocampal EEG's. From several observations of the EEG effects of ketamine in different cats, it seems reasonable to identify the ketamine-induced slow waves as representing seizure activity. Typical records of the ketamine-induced EEG seizures are presented in figures 2 and 3.

In figure 2, about 2 minutes after injecting ketamine (5 mg/kg) enhanced fast waves of the sensorimotor cortex were interrupted regularly by bursts of high-amplitude activity composed of typical spike-and-wave complexes. In the visual cortex there were also bursts of spiky waves, slightly leading in phase the spike-and-wave bursts of the sensorimotor cortex. Concurrent with these cortical events, the cat showed twitching movements of the ears, vibrissae, and some shoulder muscles. In later stages the bursts of EEG seizures became less frequent and the typical form of spike-and-wave complexes was hardly seen, even in the sensorimotor cortex.

In figure 3, the hippocampus responded to ketamine (5 mg/kg) with bursts of spike-and-wave complexes in addition to an enhancement of fast waves in the background. The sensorimotor cortical activity corresponding to the spike-and-wave burst of the hippocampus was a simple slow undulation of the baseline. Twitching movements in the periphery also occurred in this cat.

On the basis of these data, ketamine induced EEG seizures. Since degrees of sensitivity to seizure would differ from one animal to the next and from one neural site to another,

TABLE 1. Discharge Rates of 21 Units in the Sensorimotor Cortex, Recorded before and 1, 3, 5, and 10 Minutes after Injection of Ketamine*

Unit	Discharges/Sec				
	Control	1 Min	3 Min	5 Min	10 Min
1	4.4	12.8	9.4	—	8.1
2	7.0	18.0	17.5	17.8	
3	15.0	10.5	—	12.5	13.4
4	3.5	11.2	—	3.5	
5	1.9	8.0	6.5	5.1	1.8
6	15.0	20.0			
7	0.8	0	0	2.0	
8	12.0	18.8	—	13.5	15.0
9	5.5	4.3	10.5	15.5	
10	8.0	12.5	6.6	7.0	5.6
11	2.5	7.2	4.2		
12	8.0	11.5			
13	8.0	3.0	4.5	—	8.0
14	12.0	8.5	1.4		
15	4.2	21.0			
16	30.0	31.0	—	26.0	20.0
17	14.0	31.0	—	26.0	29.0
18	6.0	40.0	23.0	28.0	16.0
19	13.0	17.5	18.0	16.0	12.5
20	12.0	32.6	—	42.0	26.2
21	1.5	17.5	19.5	12.0	

* Figure 7 shows this information in graph form.

the response patterns might be expected to vary widely. Indeed, simple slow waves, spiky waves, slow waves with superimposed spikes, and spike-and-wave complexes all were observed. All were clearly distinguishable from the background of enhanced low-voltage fast waves, and in a few cats twitching of face and shoulder muscles accompanied the EEG seizures.

EVOKED POTENTIALS

Figure 4 shows potentials evoked in the visual cortex in response to single-shock stimulation of the optic chiasm. The response was a diphasic wave with small spikes superimposed on the first positive component. This configuration of the evoked potential is essentially the same as that described by previous workers.[10, 11] The control records (left column) were obtained during the state of arousal at rest, in which evoked potentials are larger than those seen during slow-wave sleep. After ketamine, 5 mg/kg, the evoked potentials in both positive and negative components gradually increased, and by 3 minutes they had almost doubled (middle column). The small spikes superimposed on the positive component were also augmented by ketamine. The evoked potentials remained enhanced as long as the background activity of low-voltage fast waves continued to be facilitated (right column). This enhancement of visual cortical evoked potentials was seen in 12 experiments on six cats.

Ketamine also enhanced the potentials evoked in the sensorimotor cortex in response to stimulation of the medial lemniscus, although the degree of enhancement was less than in the visual cortex (fig. 5). The control (left column) amplitude of the evoked potential, measured from the positive peak to the negative peak, was 250 ± 20 μv (mean $\pm$SD); three minutes after ketamine (middle column) this value was 278 ± 14 μv, and after 20 minutes it was 251 ± 15 μv (about 25 responses in each). Similar facilitation of the evoked potentials of the sensorimotor cortex was observed in four experiments on three cats.

In the stage of the maximal ketamine effect the amplitudes of evoked potentials were often much smaller than control values (an example is seen in the last record of the middle column of figure 4). Suppression of the evoked potentials, when it did occur, coincided with bursts of EEG seizure activity.

SINGLE-UNIT ACTIVITY

The sensorimotor cortex. Twenty-one units were sampled. They were found within depths of about 2 mm from the cortical surface. Amplitudes of the unitary spikes ranged from 500 μv to 3 mv. During arousal at rest the units discharged tonically at rates ranging from 1.6 to 16 spikes/sec (one exceptional unit discharged at 30 spikes/sec). No systemic studies of the changes in the discharge rate in the transition from wakefulness to sleep were made.

Ketamine increased the discharge rates in most units. Two examples are shown in figure 6-I. The discharge rates in the control state of arousal at rest were 4.4 and 13 spikes/sec, respectively. One minute after ketamine (2 mg/kg), the discharge rates increased to

13.5 and 43 spikes/sec, respectively. This facilitation lasted more than 10 minutes, subsiding gradually.

The discharge rates of the 21 units studied are shown in table 1 and plotted in figure 7 as a function of time after injection of ketamine, 2 mg/kg. In 11 of the 21 units unitary discharge was recorded for 10 minutes; in the remainder it was lost before then. It is clear that the discharge rates of most units increased a minute after injection, with slow decreases in rate in the next 10 minutes. In four units, however, the discharge rates decreased after administration of ketamine.

When the EEG of the sensorimotor cortex showed seizure activity evoked by ketamine, the pattern of unitary discharges was somewhat modified (fig. 8). The ketamine-induced EEG seizure consisted of a burst of spiky waves, during which the previously-accelerated unitary activity was completely silenced. Despite the seizures, the overall unitary discharge rate was higher than the control value.

In some units which responded to tactile stimulation of the skin, ketamine increased the numbers of spikes in response to stimulation. A typical record is given in figure 6-II.

The visual cortex. Twenty-two visual cortical units were studied. Their depths and amplitudes of spike discharges were about the same as those in the sensorimotor cortex. However, the spontaneous discharge rates were much slower in the visual cortical units.

The effects of ketamine were quite variable from one unit to another. Figure 9 illustrates activity of five different units in the same cat before and 1–3 minutes after ketamine, 2 mg/kg. In units 13 and 17, groups of several spikes, each with high-amplitude slow waves, were elicited. On the other hand, activity in some units (16, 18, and 19) was suppressed during the bursts of high-amplitude slow waves.

The EEG pattern during intervals between bursts of high-amplitude slow waves consisted of enhanced fast waves. In the burst intervals unit 16 showed a train of high-frequency discharges. In other units, however, the activity during the burst intervals remained about the same as the control value. This is typically seen in unit 17, which had a relatively high discharge rate before ketamine.

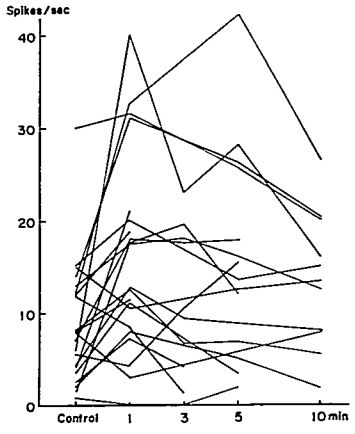

FIG. 7. Facilitation of spontaneous discharge of sensorimotor cortical units. *Ordinate,* spike counts per second. *Abscissa,* times after injection of ketamine, 2 mg/kg. Number of units, 21. In 11 of the 21 units discharge was recorded for 10 minutes, and in the remainder, for shorter periods.

The effects of ketamine on responsiveness of the units to visual stimulation were difficult to appraise. However, there are examples (units 18 and 19) in which responses to a moving shadow were more or less suppressed by ketamine. There were no units in which ketamine clearly facilitated the unitary responses to visual stimulation in any experiment.

Discussion

The most consistent electrographic signs of ketamine anesthesia in unrestrained cats were observed in the EEG's of both the neocortex and the hippocampus, which were first strongly desynchronized and then interrupted by seizure activity manifested as slow waves, slow waves with superimposed spikes, or spike-and-wave complexes. These findings were essentially the same as those of Miyasaka and Domino.[2] However, these workers did not pay much attention to EEG desynchronization, and their interpretation of the nature of the

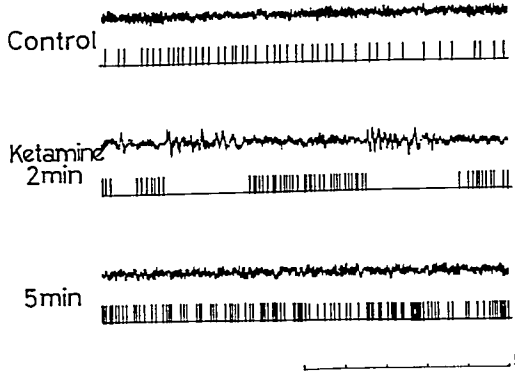

FIG. 8. Suppression of spontaneous discharges of a sensorimotor cortical unit during bursts of EEG seizures. In each row the upper record is the background EEG, the lower one spontaneous unitary discharges. Control records were obtained during arousal at rest. Ketamine, 10 mg/kg, was given in this experiment. EEG seizures were evidenced as trains of spiky waves (*middle row*). During seizure bursts the previously-accelerated unitary discharges stopped completely. At 5 minutes (*bottom row*) unitay activity was still facilitated. Unitary spikes were recorded through a Schmitt circuit.

slow waves with high amplitudes was different from ours.

Ketamine-induced neocortical desynchronization was greater than that seen during arousal at rest, and was associated with enhancement of the primary evoked potentials of the sensorimotor and visual cortices. The latter is consistent with the well-established fact that the cortical evoked potentials in response to specific thalamic volleys are increased in amplitude when cortical desynchronization is brought about by waking from slow-wave sleep in chronic cats [12-15] or by activation of the midbrain reticular formation and hypothalamus in acute cats.[16-18]

Ketamine-induced desynchronization in the sensorimotor cortex was associated with increases of the discharge rates in most of the cells. This is in accord with the findings that when EEG desynchronization occurs with behavioral arousal from slow-wave sleep, overall cell activity in the motor cortex,[19] association cortex,[20] hippocampus,[5] lateral geniculate body [21, 22] and midbrain reticular formation [23] increases. In the visual cortex, however, units in which the discharge rates increased in association with EEG desynchronization by ketamine were rare. According to Evarts *et al.*[24] and others,[25] the mean discharge rate in a group of visual cortical units does not change significantly in the transition from slow-wave sleep to arousal, although most units have slower activity during arousal than during slow-wave sleep. This suggests that in the visual cortex EEG desynchronization is not reflected in an increase of overall cell activity. This is probably true with ketamine-induced EEG desynchronization.

Since the first observation by Green and Arduini,[26] it has been well-known that during arousal when the neocortex has desynchronized, the hippocampus produces hypersynchronous slow waves (theta waves). However, it has often been reported that instead of theta waves, low-voltage fast waves occur in response to arousal stimuli.[27-29] Stumpf [30] has shown in rabbits that very strong stimuli applied to the midbrain reticular formation evoke low-voltage fast waves with concurrent depression of on-going theta waves in the hippocampus. This leads us to conclude that the hippocampal desynchronization seen early after ketamine and accompanied by strong neocortical desynchronization is a sign that the hippocampus is receiving an unusually strong activation. It should also be noted that at no stage of ketamine anesthesia did the hippocampus produce regular, slightly accelerated theta waves like those seen during paradoxical sleep. The ketamine-anesthetized state is entirely different from paradoxical sleep.

Miyasaka and Domino emphasized that keta-

mine anesthesia was characterized by the appearance of slow waves of high amplitude in the neocortex and some subcortical nuclei. Some of their findings were confirmed in the present experiment, but there are some differences. For example, the ketamine-induced slow waves were more continuous and persistent in their experiment than in ours. Also, while they did not report slow waves in the hippocampus, we found in some experiments that this structure produced slow waves with about the same pattern as those produced by the neocortex. One possible reason for these discrepancies may be that most of the experiments in the previous study were done on acute immobilized cats, whereas our cats were minimally restrained or allowed to move about freely.

Based upon our observations as well as the data of Miyasaka and Domino, we consider it more appropriate to categorize the ketamine-induced slow waves and their variants as representing EEG seizures, for the following reasons.

1) Ketamine-induced slow waves from different areas of the neocortex and hippocampus are synchronous. Miyasaka and Domino reported that this synchronism existed between the neocortex and some subcortical nuclei. Such generalized synchronism is most pertinent to the generalized seizure.

2) Ketamine-induced slow waves are often associated with sharp spikes and sometimes appear as the spike-and-wave complex which is one of the typical patterns of EEG seizures. This was also evident in the records made by Miyasaka and Domino (see their fig. 3).[2]

3) In some visual cortical units the discharges were found to burst in synchrony with the ketamine-induced slow waves with superimposed spikes. This discharge pattern is quite similar to that seen when the cat cere-

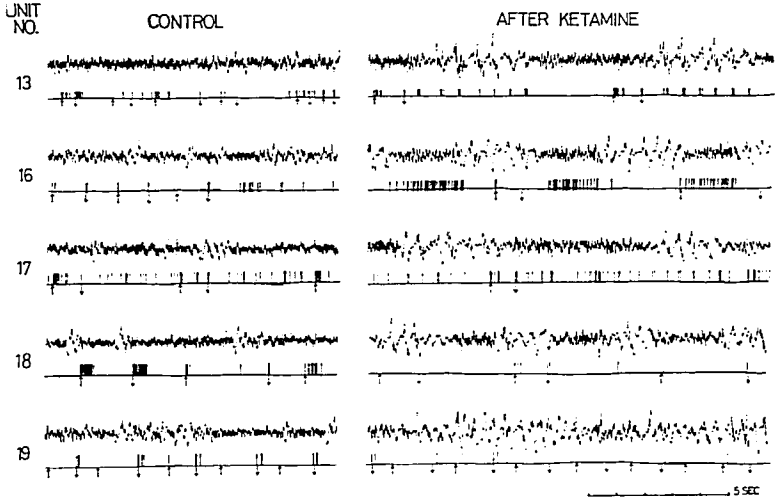

FIG. 9. Effects of ketamine on unitary activity of the visual cortex. *Left*, control records obtained during arousal at rest. *Right*, 1–3 min after injection of ketamine, 2 mg/kg. In each row the upper record is the background EEG and the lower one, unitary spikes shaped by a Schmitt circuit. Arrows below the unitary spikes indicate stimulation by a moving shadow. Changing directions of the arrows mean that the direction of the shadow was changed (see text).

bral cortex responded to low-frequency stimulation of the thalamic intralaminar system with a burst of the spike-and-wave complex.[31, 32]

So far, we have pointed out that the electrographic signs of ketamine anesthesia are EEG desynchronization and seizure activity. These two kinds of electrical activity are unlikely to be independent of each other. In the neocortex an excitatory drive produced by ketamine causes EEG desynchronization first. Although this desynchronization could be expected to be accompanied by facilitation of spontaneous unitary discharges, such facilitation was more evident in the sensorimotor cortex than in the visual cortex. Correspondingly, facilitation of the unitary responses to peripheral stimulation was conspicuous in the sensorimotor cortex only. In addition, if certain critical conditions, local and/or general, are fulfilled, seizure activity with various electrical patterns during which unitary activity tends to be suppressed develops. That excessive excitation often leads to blocking of single-unit activity has been demonstrated in unitary studies of the seizure activity induced by electrical and chemical stimulation.[23-37] Although our study of hippocampal activity during ketamine anesthesia was limited, it is not unreasonable to suppose that the above-mentioned process of ketamine action may be operative in the hippocampus as well.

Domino and associates[1] maintain that there is a functional dissociation between the thalamo-neocortical and limbic systems during ketamine anesthesia. If their concept of functional dissociation means that ketamine acts differentially on the two systems, we do not support it, because in the present experiment the actions of ketamine, both EEG-desynchronizing and seizure-inducing, were found to affect the neocortex and the hippocampus equally.

Winters and associates[38, 39] have presented the view that EEG changes induced by increasingly more potent central nervous system excitants constitute a continuum of desynchronization, intermittent hypersynchrony, continuous hypersynchrony, spikes, spikes with electrical silence, and generalized seizure. These workers pointed out that some drugs used for anesthesia (N_2O, alpha-chloralose, gamma-hydroxybutyrate, ether, and trichloroethylene) have EEG effects corresponding to various stages in the above-mentioned continuum. Phencyclidine, 1-(1-phenylcyclohexyl) piperidine hydrochloride, was found by Winters *et al.*[38] to induce generalized seizures, the extreme of the EEG excitation continuum. Although ketamine and phencyclidine have similar chemical structures, ketamine's EEG effects are limited to intermittent hypersynchrony, including desynchronization. It is evident that the clinical usefulness of this drug as a general anesthetic is based upon a mechanism entirely different from that of the barbiturates.

Finally, a brief comment about the correlation between behavioral and electrographic signs of ketamine anesthesia is indicated. First, EEG desynchronization may be a basis for behavioral arousal. Salivation, licking, and searching behavior may be correlated with excitation of the limbic system, because these behavioral signs are known to be elicitable by electrical stimulation of any part of the limbic system.[6, 7] The motor symptoms, such as stretching of the forelimbs, slow movements of the head, and opisthotonus, are likely to be due to excitation of the extrapyramidal motor system, because Miyasaka and Domino found that the caudate nucleus was affected by ketamine and showed hypersynchronous slow waves. The last question is concerned with loss of consciousness. The present experiment has shown that during ketamine anesthesia the seizure activity induced has various electrographic patterns. Although the ketamine-induced EEG seizure does not lead to generalized convulsions, it may interfere with consciousness in the same way as petit mal seizures.[40]

The authors are grateful to Prof. Hiroshi Takeshita for his constant encouragement. Many thanks are due to Drs. S. Kiyono and H. Noda for their helpful advice during the course of the experiment.

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Neonatology

NEONATAL MORTALITY: THE MALE DISADVANTAGE In 2,735 consecutive newborn autopsies, the ratio of males to females was 1.28:1, which differed significantly from the 1.05:1 ratio for all livebirths in the United States. There was a near-equal male-to-female ratio for most disorders in the stillborn infants, while disorders arising after birth had a preponderance among male infants. The stillborn ratios presumably reflect a predominant maternal influence, while birth and removal from the maternal environment uncovers an inherent biologic disadvantage of being male, a disadvantage not selectively related to specific disease processes. This nonspecificity is confirmed by the finding of several disorders in which sex ratios for stillborns are quite different from the ratios recorded for liveborn infants. This sex ratio for liveborn Caucasians was significantly greater than that for nonwhites, and the non-poor had a significantly greater ratio than the poor. About half of these differences appear related to a greater incidence of prenatal bacterial infections in the poor and nonwhites. This study reaffirms the finding, suggested on clinical grounds in the past, that male infants have a greater risk of neonatal death than females. (*Naeye, R. L., and others: Neonatal Mortality, the Male Disadvantage, Pediatrics 48: 902–906, 1971.*)