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Anticonvulsant Actions of Enflurane on Epilepsy Models in Cats

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The effects of enflurane on three epilepsy models were studied in cats. The models used were seizures in amygdaloid kindled cats and those induced by bicuculline and penicillin. The authors found that not only a subconvulsive (1.5%) but a convulsive (3.5%) dose of enflurane suppressed the seizures in all models. There was no sign of activation by enflurane of the epileptic focal activities in the dose range studied: the penicillin-induced cortical seizure was suppressed completely, and the threshold dose of bicuculline required to induce seizure in normal cats and the threshold current required to induce seizure in amygdaloid-kindled cats were both increased by both the subconvulsive and convulsive dose of enflurane. The pattern of suppression was, however, dissimilar in each model. It was dose dependent in the case of penicillin-induced seizure, while it was biphasic in several aspects in the seizures of bicuculline-induced and amygdaloid kindled models. For the subconvulsive dose the degrees of increase in the thresholds required to induce seizure in bicuculline-induced and amygdaloid-kindled models were both greater than those for the convulsive dose of enflurane. In spite of such a definite suppression of the excitability of focus, the propagation of amygdaloid after-discharge was facilitated by the convulsive dose. The intensity of convulsion induced by suprathreshold dose of bicuculline was depressed in a dose-related manner. The intensity of the convulsion in the amygdaloid-kindled model was also suppressed when it was estimated by visual inspection of behavior and the degree of activation of the brain electrical activities. The authors conclude that there is little, if any, exacerbation by enflurane of preexisting epileptic foci, the only exception possibly being the case of certain myoclonic type epilepsies such as progressive myoclonic epilepsy and photosensitive epilepsy. This anesthetic probably can be used with a considerable degree of safety for epileptic patients. (Key words: Anesthetics, volatile: enflurane. Brain: EEG; reticular multi-unit activity; convulsions; anticonvulsant actions. Complications: convulsions.)

SINCE 1935, when von Meduna[1] first measured the convulsive threshold of pentylenetetrazol in epileptic patients, a number of confirmatory works appeared, and a consensus was reached that convulsants, such as pentylenetetrazol and bemegride, can produce seizures more easily in epileptic than in normal individuals.[2–4] For a period, these drugs became widely used to differentiate epileptic from nonepileptic conditions, but since the distinction between the "normal" and "abnormal" was not always clear, the technique gradually fell into disuse. Nevertheless, the higher susceptibility of epileptic patients to these drugs is still valid, and at present, this technique is of occasional value for the accentuation and identification of focal epileptic discharges.[5]

Many investigators have shown that by using relatively high concentrations (up to 3.5%) and hypocarbia, enflurane can induce seizure,[6] and some have advised avoidance of use of this anesthetic for epileptic patients.[7,8] Although pentylenetetrazol or bemegride and enflurane have this convulsive property, there are fundamental differences in their pharmacologic actions: the site of action of pentylenetetrazol and bemegride is considered to be on GABA receptor or GABA-mediated chloride ionophore activity, thus blocking the ionic basis of central nervous system (CNS) inhibitory synapses, and its net CNS action is excitatory in nature (Pellmar and Wilson, 1977),[9] while various CNS suppressive actions have been described for enflurane, *e.g.*, the cerebral oxygen consumption,[10] reticular neuronal firing,[11] cerebral glucose utilization[12] are suppressed. Further, anticonvulsive or antiepileptic actions have also been noted with enflurane in laboratory animals[13] and humans.[14–16] These studies, however, had limitations in that the anesthetic concentrations studied were restricted within the range of subconvulsive dose[13–15] or the patients were kept on routine anticonvulsants.[14–16] These studies did not necessarily rule out the possible facilitation by a convulsive dose of enflurane of the patient's preexisting epileptic foci, since the anticonvulsants used in these studies suppressed the patient's focal activities to various degrees and may well derange their normal responses to the convulsant action of enflurane. The present study was designed to investigate the action of enflurane, in both convulsive and nonconvulsive concentrations, on three types of epilepsy models: the amygdaloid kindled animal, penicillin-induced cortical epileptic activity and bicuculline-induced generalized seizure. Our goal was to define the safety or danger of this agent in these models and thereby suggest the possible clinical application of enflurane use in anesthesia for epileptic patients.

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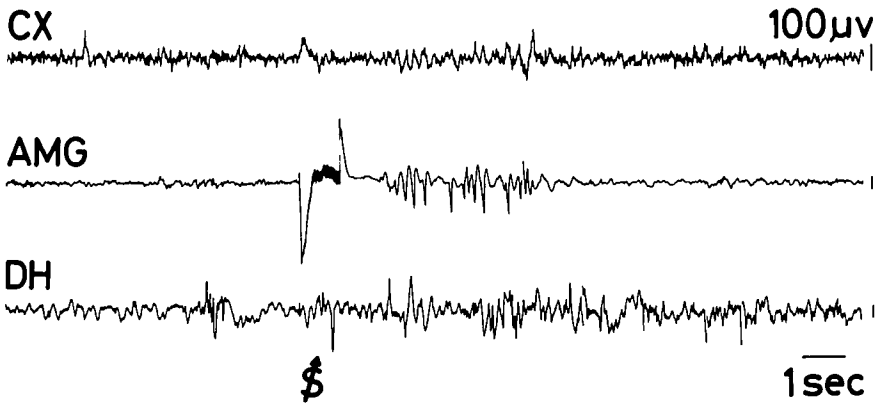

FIG. 1. Amygdaloid after-discharge. CX = anterior suprasylvian gyrus; Amyg = nucleus amygdalae medialis; DH = formatio hippocampalis dorsalis. The aymgdala, ipsilateral to the recording site, was stimulated by a high-frequency constant current of 60 Hz, 250 μA for 1 s. This figure was recorded on the first day of amygdaloid stimulation. Note after-discharge of a short period appearing in the amygdaloid EEG.

Materials and Methods

A total of 24 cats of either sex, weight 3.5–4.8 kg, were used for the three different models of epilepsy.

AMYGDALOID KINDLED CATS

Seven cats with chronically implanted brain electrodes were used. The surgical procedures were performed under pentobarbital anesthesia, 40 $mg \cdot kg^{-1}$ ip, and the electrodes were implanted over the anterior suprasylvian gyrus, and in the medial amygdala (two electrodes in A 12 and 10; L 9; H −6), dorsal hippocampus (A 2; L 8; H +9), and midbrain reticular formation (A 3; L 3; H −1) according to the atlas of Snider and Niemer.[17] The electrode positions were verified histologically after the experiments. The cortical surface electrodes consisted of stainless steel screws of 2.0 mm diameter, drilled so as to reach the dura but not to penetrate. A reference electrode was placed in the frontal bone. The subcortical electrodes consisted of side-by-side stainless steel wires, 0.2 mm diameter, insulated with epoxylite resin except for the cut end, the tips having a vertical separation of 0.5–1.0 mm. All leads were soldered to a miniature vacuum tube socket, which was fixed to the skull with dental cement. During the experiment, the socket was connected to the recording devices and an electric stimulator with a bundle of flexible cables of 1.5 m length to allow for free movement of the animals.

Establishment of Kindling Model: Daily electric stimulation of 60-Hz, 1-s duration was given through one of the amygdaloid electrodes, utilizing a constant current stimulator and isolating unit (Sanei® 3F46 and 5361). On the first experimental day, the stimulating current was set at 50 μA initially and was then increased by 50 μA at 15-min intervals until local after-discharge could be induced in the amygdaloid EEG (fig. 1). From the second experimental day, the amygdaloid stimulation at this current was given once a day until the amygdaloid after-discharge propagated to the dorsal hippocampus and then to the cerebral cortex to form a generalized seizure, showing a march of ictal phenomena ending with a generalized convulsion. When this generalization of the after-discharge could be induced consistently at each successive 5-day trial, the so-called kindled state was considered to have been established (for further details, see Wada and Sata[18]).

The Action of Enflurane on the Propagation of Amygdaloid After-discharge: Of the seven kindled cats, prepared as above, six were used in this study. They were anesthetized initially with enflurane, 4% in oxygen, in an anesthesia box, and after reaching a moderate level of anesthesia, the trachea was intubated. The inhaled enflurane concentration was then set either at 1.5% (light anesthesia: subconvulsive dose) or 3.5% (deep anesthesia: convulsive dose) and was maintained for 30 min. Electrical stimulation was then given at the amygdaloid nucleus with the same current as used to establish the kindled state, which was above threshold once the kindled state was established. The behavioral and electrical activities of the seizure during enflurane anesthesia were compared with those of the control unanesthetized period. The actions of the different concentrations were studied with an interval of at least 7 days between exposures.

Enflurane Action on the Threshold Current to Induce Seizure: The kindled cats, prepared and used as above, were used in this study. Of the seven cats, two died of status epilepticus during this study, and data were collected from the remaining five cats. The stimulating current was decreased from that used in the above study by 25-μA steps daily until the stimulation failed to induce generalized seizure in nonanesthetized state, and a current of 25 μA above the maximum current that did not induce seizure was taken as the control threshold level. During anesthesia with a convulsive concentration of enflurane (3.5%) for 30 min, the induction of seizure by amygdaloid stimulation was attempted. On the first day of drug study, the current was set at the threshold

level previously determined. When the amygdaloid stimulation failed to induce seizure, the stimulating current was increased by 25-μA increments at each experimental session until a generalized seizure occurred. This trial of amygdaloid stimulation was also performed, with 7-day intervals between each amygdaloid stimulation.

Bicuculline-induced Seizure

Intensity of Seizure: Six cats with chronically implanted brain electrodes were used. The procedures of brain electrode implantation were identical to those used for the amygdaloid kindling study, except that in this group of cats there was only one amygdaloid electrode. On the day of drug study, the cat was initially anesthetized with enflurane by insufflation. A polyethylene cannula, 1.0 mm in external diameter, was inserted into the inferior vena cava through the femoral vein with the aid of 16-gauge Argyle Medicut®. The catheter was fixed to the body with adhesive tape and the remaining venous line to the bundle of recording cables. Two hours later, when full recovery from anesthesia was confirmed by visual inspection of CNS electrical activities and behavior, a control response to intravenous bicuculline, 0.2 $mg \cdot kg^{-1}$, was obtained. In the study of enflurane actions, the trachea was intubated, following enflurane anesthesia by insufflation, and then the enflurane concentration was set at either 1.5 or 3.5%. After maintenance at each concentration of enflurane, on separate occasions, for 30 min, bicuculline, 0.2 $mg \cdot kg^{-1}$ iv, was administered again, and the electrical and behavioral responses were observed. Each experiment was performed at 7-day intervals, and the action of different enflurane concentrations was evaluated by comparing the values obtained on different experimental days.

Threshold Dose: Three of the five cats used above and an additional newly prepared three cats were used. Preliminary studies showed that a slow intravenous infusion of bicuculline to enflurane-anesthetized cats induced a gradual lightening of the level of anesthesia, and the cough reflex so provoked seemed to induce generalized seizure with even a very small dose of bicuculline. Therefore, paralyzed cats were used for this study. After inserting a femoral venous catheter, under enflurane anesthesia, the trachea was intubated with the aid of alcuronium iv (initial dose 2.5 mg, supplemented as required), and the lungs were ventilated with a mechanical ventilator using 100% oxygen. Approximately 2 h later, when the CNS electrical activities showed a normal wakefulness pattern by visual inspection, the drug study was performed. Bicuculline, 0.05 $mg \cdot kg^{-1} \cdot min^{-1}$, was administered intravenously, using a constant rate infusion pump, until an electrographic generalized seizure pattern appeared during the control state or after administering 1.5 or 3.5% enflurane in oxygen for 30 min. The effects of enflurane were assessed by changes in the background level of reticular multiunit activity, the threshold dose of bicuculline to induce seizure, the level of maximum increase of reticular multiunit activity during seizure, and the duration of electrographic seizure activity. Each drug study was performed in different experimental sessions at 7-day intervals.

Penicillin-induced Focal Activity

Five cats were used in this study. All cats initially were anesthetized with halothane, nitrous oxide, and oxygen by insufflation. The trachea was intubated with the aid of alcuronium (initial dose of 0.2 $mg \cdot kg^{-1}$ iv, supplemented as required), and respiration was controlled with a mechanical ventilator (Acoma® 100R). The succeeding surgical procedures were done under halothane (1.0% in 75% nitrous oxide in oxygen) anesthesia. The cats were mounted on a stereotaxic frame, and the brain electrodes were implanted in the anterior suprasylvian gyrus, basilar amygdala, dorsal hippocampus, midbrain reticular formation, and in the frontal bone (reference electrode). After implanting these electrodes, the anterior sigmoid gyrus of one side was exposed by removing the bone and opening the dura, and about 5,000 units of penicillin-G (bensylpenicillin) dissolved in 25 μl of saline was injected into the brain substance immediately beneath the pia mater, using a binocular microscope, for the purpose of making an epileptic focus. However, the exact dose injected could not be confirmed, since a certain volume leaked out along the needle. A parallel electrode used for the subcortical recording was inserted to approximately 1 mm depth near the penicillin-injected site, to record the focal electrical activities. Indwelling catheters were inserted into the cephalic vein for fluid and drug administration and into the femoral artery for recording arterial blood pressure and drawing blood samples for measurement of gasses. After confirming the appearance of repetitive EEG spike activities in the penicillin-injected site, the halothane–nitrous oxide–oxygen mixture was changed to room air. One hour later, the typical EEG pattern of status epilepticus of focal origin consisting of the appearance of repetitive high-voltage ictal discharges (sustained seizure) separated by interictal electrical silence and spikes appeared. After establishment of the EEG pattern of status epilepticus, enflurane in oxygen was administered in concentrations of 1.5%, and then 3.5% for 30 min, respectively. At the end of enflurane administration, when enflurane blocked the appearance of sustained seizures, repetitive tapping was given to the

back of cat, and the enflurane-induced epileptoid status was confirmed. After recovery from enflurane anesthesia, confirmed by reappearance of sustained EEG seizure, either thiamylal (5 mg·kg^{-1} iv in two cats) or diazepam (2 mg·kg^{-1} in three cats) was administered, and the effects were compared with those for enflurane.

Method of Enflurane Administration

During the study of enflurane actions, the respiration was controlled by a mechanical ventilator (Acoma® AR 100), and the end-tidal CO_2 was maintained in the range of 29–31 mmHg, utilizing an infrared CO_2 analyzer (Cavitron® PM-20N), and arterial *p*H (only in the study of penicillin-induced seizure) was maintained at 7.40–7.45 by intravenous administration of $NaHCO_3$. The rectal temperature was maintained between 38–39° C, using a warm water blanket and heating lamp. The inhaled enflurane concentration was determined by a recalibrated Enfluratec® (Cyprane) using 3 l·min^{-1} gas flow through the vaporizer, and the enflurane–oxygen mixture was administered via a nonrebreathing circuit.

Recording of CNS Electrical Activities and Data Analysis

The cortical and subcortical EEGs were recorded on an eight-channel polygraph (Nihonkoden®), and the reticular multiunit activity on a straight writing oscillograph (Sanei Rectigraph® 8s), according to our method described previously.[19,20] Briefly, the technique was as follows. The wide-band signal obtained from the preamplifier of the polygraph was introduced into a high-frequency band-pass filter, the peak frequency response of which was centered at 1,300 Hz, with 3-db decrease at 600 and 2,500 Hz. This high-frequency activity was rectified and smoothed with an electronic circuit (envelope detector) with the smoothing time constant of 50 ms and was expressed by the oscillation of DC voltage: the higher the DC level, the greater the firing of a population of units. This signal was recorded on a slow-moving oscillograph (Sanei Rectigraph® 8s) with a paper speed of 10 mm·min^{-1}. The noise level of the recording system was estimated to be the DC level obtained by inserting a 10 kΩ resistor and a short across the input in place of the animal. The signal was measured as the distance from the lower limit of the multiunit tracing to the 10 kΩ resistor line (the signal to noise ratio exceeded 10 in all cases). Since the level of multiunit activity is dependent not only on the amount of bioelectric activity but also on the impedance of the electrode, calibration of the multiunit activity level was not practical and the changes induced by enflurane were expressed as percentages of the level during the control preanesthetic state. Since the level of this activity fluctuated from time to time, it was represented as the distance from the lower limit of the trace to the 10 kΩ resistor line. The degree of activation during seizure was also measured from the lower limit of the trace prior to the occurrence of seizure to the peak observed during seizure.

The values obtained during the nonanesthetized state served as control in each experiment, and the changes induced by enflurane were expressed as a percentage of the control, mean ± SEM. The statistical methods used were Wilcoxon paired-sample test in the study of threshold current in amygdaloid kindled cats, and Bonferroni's multiple comparison performed after the repeated-measure analysis of variance in the remaining studies.

Results

Amygdaloid Kindled Model

The daily electrical stimulation of the amygdaloid nucleus in our cats induced progressive developments of seizure identical to those reported by Wada and Sata.[18] The kindling process was completed within 13–38 days (24 ± 3.5, mean ± SEM) in all cats. The seizure consisted of six distinguishable sequential stages, culminating in a generalized convulsion. The total duration of seizure ranged from 42 to 114 s (75 ± 13.1 s). At the outset, the stimulation produced either no behavioral manifestation or only slight facial twitching ipsilateral to the site of stimulation. The chronologic pattern of this seizure development was represented by the unilateral facial twitching ipsilateral to the stimulation (stage 1), followed by bilateral facial twitching (stage 2), head-nodding (stage 3), contralateral head turning with tonic extension of contralateral forepaw and circling (stage 4), generalized clonic jerking (stage 5), and finally generalized convulsion (stage 6) (figs. 2 and 3). The development of this seizure manifestation was displayed by the march of events in the above-described order, although the individual stages were not always apparent on visual inspection because of the rapid progress. During the progression from stages 1 to 6, the amygdaloid after-discharge propagated initially to the dorsal hippocampus and then to the cortex, and this propagation was represented initially by high-frequency, low-amplitude repetitive spikes, which increased gradually and finally reached the maximum amplitude at stage 6. The termination of the ictal EEG was represented by a sudden appearance of isoelectric pattern or low-amplitude rhythmic slow waves. The reticular multiunit activity showed a gradual increase from stage 1, reaching a

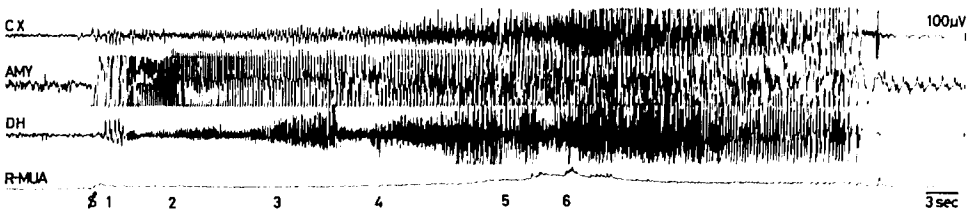

FIG. 2. Pattern of amygdaloid after-discharge propagation in a kindled cat. R-MUA = multiunit activity of midbrain reticular formation. Cx = anterior suprasylvian gyrus; Amyg = nucleus amygdalae medialis; DH = formatio hippocampalis dorsalis. The numbers below the trace indicate behavioral seizure stages corresponding to figure 3. The amygdaloid after-discharge propagated to the dorsal hippocampus and then to the cortex.

maximum level at the early period of stage 6, and a decrease followed by a concomitant postictal EEG suppression, to the level in between the prestimulus and the ictal maximum level, after which the prestimulus levels gradually returned (fig. 4, control). The maximum level of increase during seizure was 182.7 ± 20.9% of that of the prestimulus period. During establishment of the kindling, all cats became increasingly restless and polyphagic.

Propagation of Amygdaloid After-discharge: The effects of enflurane on the amygdaloid stimulation-induced seizure in kindled cats are summarized in table 1. During light anesthesia (1.5% enflurane), the background EEG was represented by irregular slow waves in all recorded areas and occasional spikes in the limbic structures (fig. 5). During deep anesthesia (3.5% enflurane), it was represented by occasional spikes appearing on an otherwise isoelectric EEG. Such were associated with a progressive and significant decrease of background reticular multiunit activity (fig. 4). During light anesthesia, the distant propagation of stimulation-produced amygdaloid afterdischarge was suppressed, and the involve-

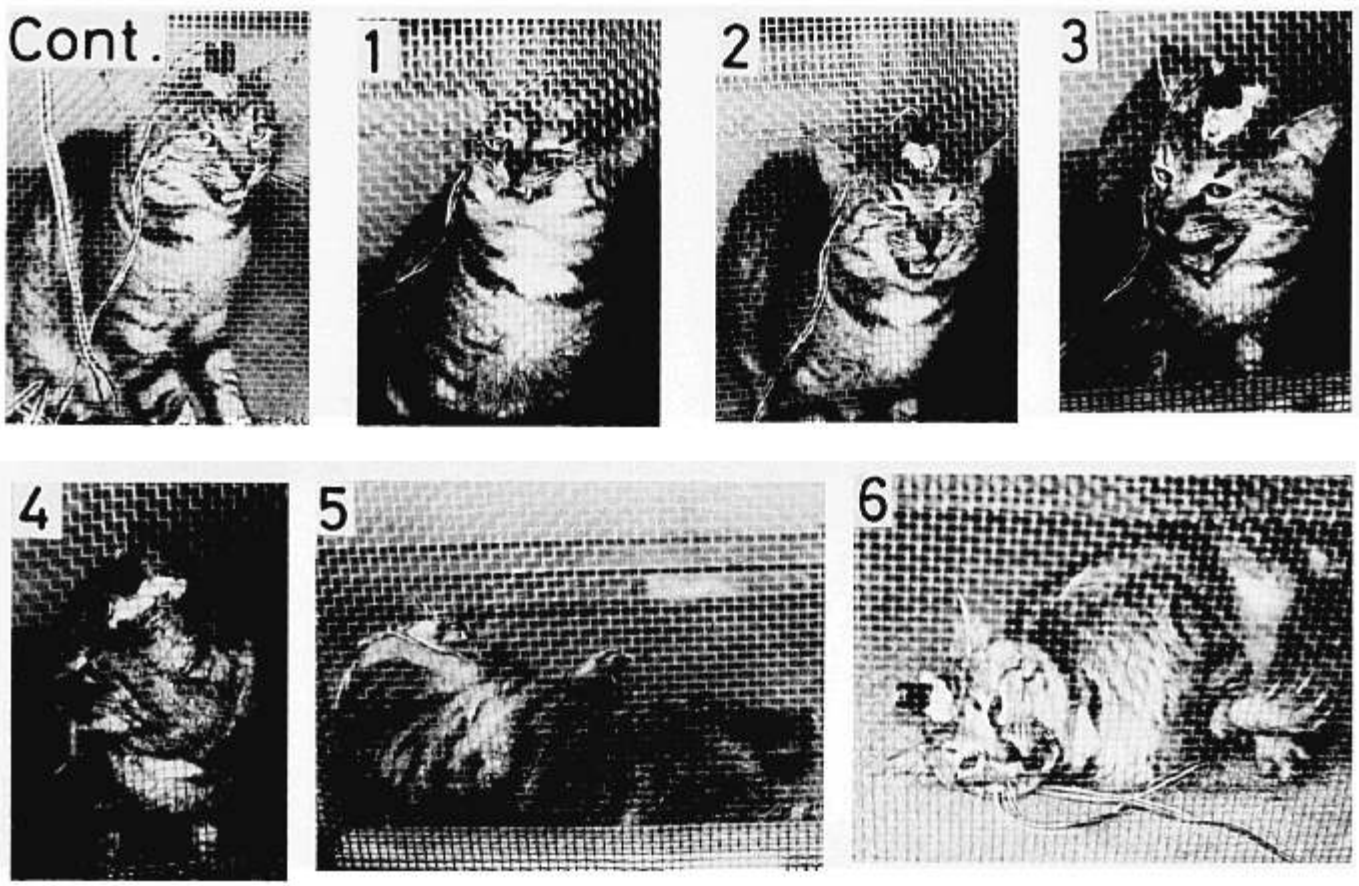

FIG. 3. Behavioral seizure stages corresponding to EEGs in figure 2. All stimulating and recording electrodes were implanted on the left side. See text for explanation of each stage.

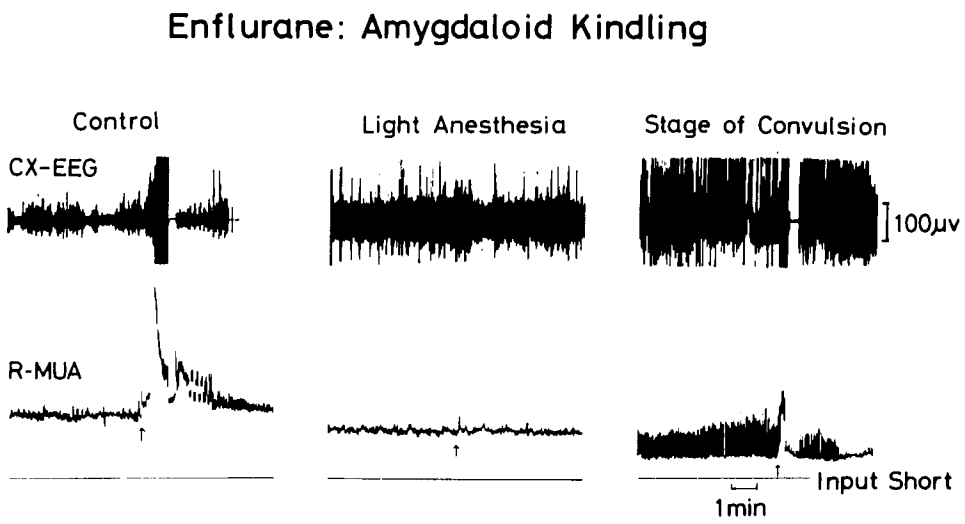

FIG. 4. Effects of enflurane on the generalized seizure in an amygdaloid-kindled cat. CX = EEG of anterior suprasylvian gyrus; R-MUA = multiunit activity of midbrain reticular formation. Arrows indicate the stimulation of amygdala. This figure corresponds to figure 5 and shows EEG and reticular multiunit activity recorded with a slow-moving oscillograph. The upward shift of the trace of reticular multiunit activity indicates increase in reticular neuronal firing. Light anesthesia (1.5% enflurane in oxygen) blocked propagation of after-discharge to the cortex and midbrain reticular formation, and no enhancement of reticular neuronal firing was induced by the amygdaloid stimulation. Only a stimulation artefact was obtained. Deep anesthesia (3.5% enflurane in oxygen) did not block the propagation of after-discharge but did suppress the magnitude of enhancement of reticular neuronal firing. Compare the EEGs of figure 5.

ment of whole brain by the seizure was seen only in one cat. In the remaining cats, it propagated only to the dorsal hippocampus, leaving the cortical EEG unaffected. Such limbic seizures, lasting 20.7 ± 4.9 s, were shorter than the control generalized seizure ($P < 0.001$). The increase of reticular multiunit activity associated with the seizure was also smaller than that of the control generalized seizure ($P < 0.001$). Behavioral convulsion was seen only in one cat in which the afterdischarge propagated to the cortex. The severity of convulsion was also depressed, showing only tonic extensions of the forepaw of short duration.

During deep anesthesia, the distant propagation of amygdaloid afterdischarge was facilitated in that the progression of the sequential stages of seizure from 1 to 5 disappeared, and the final stage of generalized convulsion, *i.e.*, stage 6, appeared immediately following the amygdaloid stimulation in all cats. However, the

TABLE 1. Enflurane Actions on the Seizure of Amygdaloid Kindled Cats

Cat No.		1	2	3	4	5	6	m ± SEM	*P* Value
Control									
MUA increase by seizure	(%)	100	100	100	100	100	100	100	
Duration of seizure	(s)	64	114	54	68	108	42	75.0 ± 13.1	
	(%)	100	100	100	100	100	100	100	
Preseizure MUA level	(%)	100	100	100	100	100	100	100	
1.5% enflurane									
MUA increase by seizure	(%)	18.2	17.5	6.4	21.4	21.0	10.8	15.9 ± 2.7	*
Duration of seizure	(s)	20	25	0	29	30	20	20.7 ± 4.9	
	(%)	31.0	21.9	0	42.6	27.8	47.6	28.5 ± 7.6	*
Preseizure MUA level	(%)	78.3	80.6	85.0	93.3	89.2	79.4	84.3 ± 2.7	†
3.5% enflurane									
MUA increase by seizure	(%)	49.1	98.2	6.4	33.3	76.4	17.2	46.8 ± 15.8	†‡
Duration of seizure	(s)	19	41	0	28	30	10	21.3 ± 6.6	
	(%)	29.7	36.0	0	41.2	27.8	23.8	26.4 ± 6.4	*
Preseizure MUA level	(%)	34.8	35.5	40.0	60.0	51.4	33.8	42.6 ± 4.8	*§

* $P < 0.001$ *versus* control.
† $P < 0.01$ *versus* control.
‡ $P < 0.05$ *versus* 1.5% enflurane.
§ $P < 0.001$ *versus* 1.5% enflurane.

intensity of convulsion appeared markedly suppressed on visual inspection. The level of maximum increase of reticular multiunit activity by seizure was statistically greater than that of light anesthesia ($P < 0.05$) but smaller than that of control ($P < 0.01$).

Threshold Current to Induce Seizure: Since the above study showed a definite increase by light anesthetia in the threshold current required to induce seizure, the study of drug actions on the threshold current was performed, only under conditions of deep anesthesia (3.5%). The results are summarized in table 2. The threshold was elevated significantly ($P < 0.05$).

Bicuculline-induced Seizure

Intensity of Seizure: The effects of enflurane on the convulsant action of bicuculline are summarized in table 3. Bicuculline, 0.2 $mg \cdot kg^{-1}$ iv, induced EEG seizure consisting of repetitive high-frequency high-amplitude spikes, lasting for 157.6 ± 59.7 s and terminating with a sudden appearance of postictal electrical silence. The EEG seizure was associated with initially tonic and then clonic type convulsion and an enhancement of reticular multiunit activity by 248.2 ± 18.4% of the predrug background level. Enflurane suppressed the bicuculline-induced seizure: the light anesthesia decreased the duration of seizure to 32.8 ± 18.1% of control ($P < 0.05$ *vs.* control) and the deep anesthesia to 18.3 ± 4.6% of control ($P < 0.05$ *vs.* control; n.s. *vs.* 1.5% enflurane). The enhancement of reticular multiunit activity was also suppressed: it was 66.0 ± 12.9% of control ($P < 0.05$ *vs.* control) during light anesthesia and 65.6 ± 4.8% of control during deep anesthesia (fig. 6) ($P < 0.05$ *vs.* control, n.s. *vs.* 1.5% enflurane). The intensity of convulsion was also suppressed on visual inspection. All these changes induced by enflurane were associated with significant and progressive decreases of background reticular multiunit activity to 54.5 ± 9.3% of the control with light anesthesia ($P < 0.001$ *vs.* control) and 25.3 ± 7.4% with deep anesthesia ($P < 0.001$ *vs.* control, $P < 0.01$ *vs.* 1.5% enflurane).

Threshold Dose: The effects of enflurane on the threshold dose of bicuculline required to induce seizure are summarized in table 4. Enflurane increased the threshold dose. The increase by light anesthesia was significantly greater than that of deep anesthesia ($P < 0.01$ *vs.* control; $P < 0.05$ *vs.* 3.5% enflurane), and the increase by deep anesthesia was not significant (*vs.* control). The maximum increase of reticular neuronal firing by seizure and the duration of seizure were both suppressed in a dose-related manner: the suppression by deep anesthesia ($P < 0.001$ *vs.* control) was greater than that by light anesthesia ($P < 0.001$). The suppression of these parameters was associated with a dose-related suppression of the background level of reticular neuronal firing ($P < 0.001$, 1.5% enflurane *vs.* control; $P < 0.001$, 3.5% enflurane *vs.* 1.5% enflurane).

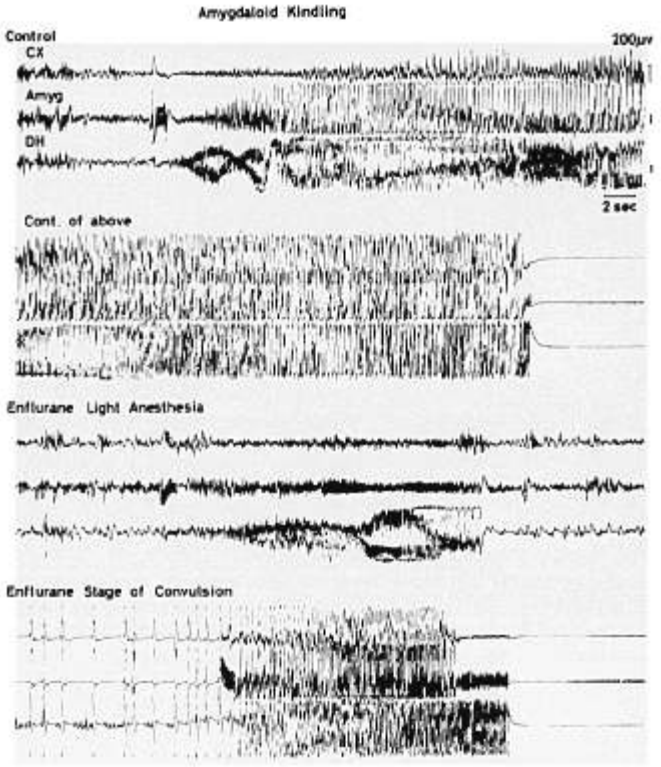

FIG. 5. Effects of enflurane on the propagation of amygdaloid after-discharge in an amygdaloid-kindled cat. CX = anterior suprasylvian gyrus; Amyg = nucleus amygdalae medialis; DH = formatio hippocampalis dorsalis. Amygdaloid stimulation is not indicated in the figure but can not be noted by the artefacts in the amygdaloid trace. Light anesthesia (1.5% enflurane in oxygen) induced synchronization of background EEG and suppressed propagation of seizure to the cortex. Deep anesthesia (3.5% enflurane) induced spikes and electrical silence in the background EEG and facilitated the propagation of seizure. The total duration of seizure was shortened. See text for further details.

Penicillin-induced Seizure

Following recovery from halothane anesthesia, there was an EEG pattern of status epilepticus in all cats: the

TABLE 2. Enflurane-induced Changes in Threshold Current Required to Induce Seizure in Kindled Cats

Cat No.	Control	Anesthesia
1	250 (μA)	300 (μA)
2	150	200
3	100	300
4	200	325
5	300	Over 1,000

TABLE 3. Enflurane Actions on the Bicuculline-induced Seizure in Cats

Cat No.		1	2	4	5	6	m ± SEM	*P* Value
Control								
Duration of seizure	(s)	292	284	57	85	70	157.6 ± 59.7	
	(%)	100	100	100	100	100	100	
MUA increase by seizure	(%)	100	100	100	100	100	100	
Preseizure MUA level	(%)	100	100	100	100	100	100	
1.5% Enflurane								
Duration of seizure	(s)	3	35	5	71	41	31.0 ± 14.1	*
	(%)	1.0	12.3	8.8	83.5	58.6	32.8 ± 18.1	
MUA increase by seizure	(%)	33.9	92.9	46.2	68.4	88.7	66.0 ± 12.9	*
Preseizure MUA level	(%)	57.1	81.8	32.0	57.6	44.0	54.5 ± 9.3	†
3.5% Enflurane								
Duration of seizure	(s)	30	23	12	26	15	21.2 ± 3.8	*
	(%)	10.3	8.1	21.1	30.6	21.4	18.3 ± 4.6	
MUA increase by seizure	(%)	78.0	66.1	51.9	62.0	69.8	65.6 ± 4.8	*
Preseizure MUA level	(%)	9.5	40.9	12.0	24.2	40.0	25.3 ± 7.4	†‡

* $P < 0.05$ *versus* control.
† $P < 0.001$ *versus* control.
‡ $P < 0.01$ *versus* 1.5% enflurane.

EEG pattern consisted of sustained (range 10–50 s, mean 32.4 ± 6.5 s) appearance of repetitive high-voltage spikes (sustained seizure) separated by low-voltage EEG activity with interictal spikes (fig. 7). The sustained seizures were associated with an increase of reticular multiunit activity, 168.1 ± 22.1% of the background interictal level. Administration of enflurane suppressed the occurrence of the sustained seizures, while it increased the frequency of interictal EEG spikes in a concentration-dependent manner (figs. 8 and 9). The sustained seizure was completely blocked by administration of 3.5% enflurane. The level of background reticular multiunit activity was also suppressed, in a concentration-dependent manner: it was suppressed to 81.2 ± 5.6% of control ($P < 0.05$ *vs.* control) at 1.5% enflurane and to 38.7 ± 9.4% at 3.5% ($P < 0.001$ *vs.* control, $P < 0.001$ *vs.* 1.5% enflurane). The increase of reticular multiunit activity associated with the sustained seizure and the interictal spikes were both depressed by enflurane. During administration of 3.5% enflurane, when the sustained seizure was completely blocked, repetitive tapping of the body induced generalized seizures lasting 23.4 ± 2.4 s in all cats.

After recovery from enflurane anesthesia, administration of either diazepam, 2 $mg \cdot kg^{-1}$ iv (three cats), or thiamylal, 5 $mg \cdot kg^{-1}$ iv (two cats), blocked the sustained

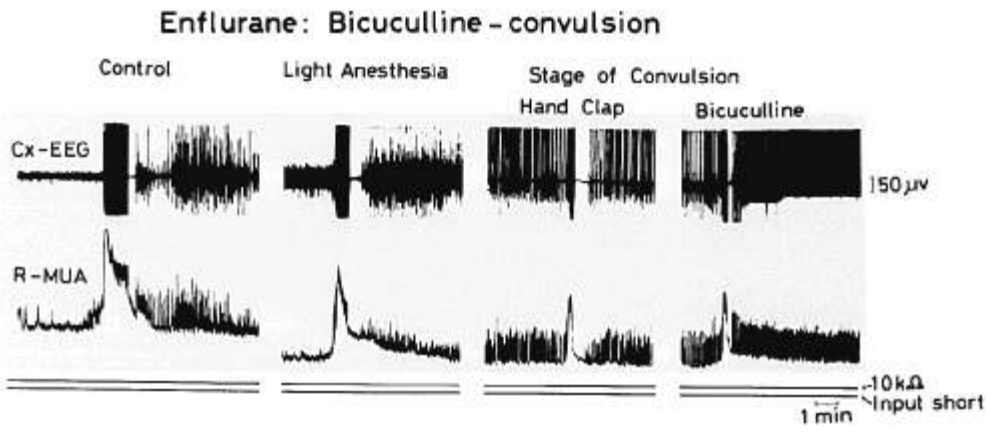

FIG. 6. Enflurane actions on the bicuculline-induced seizure. Cx = EEG of anterior suprasylvian gyrus; R-MUA = multiunit activity of midbrain reticular formation. Seizure was induced by bicuculline, 0.2 $mg \cdot kg^{-1}$, iv. Light anesthesia was induced by 1.5% enflurane in oxygen and deep anesthesia by 3.5% enflurane. The stage of convulsion was confirmed by inducing seizure by repetitive hand clapping. Enflurane induced dose-related suppression of background level of reticular multi-unit activity, duration of seizure, and activation of reticular neuronal firing during seizure.

TABLE 4. Enflurane Actions on the Threshold Dose of Bicuculline Required to Induce Seizure

Cat No.		1	2	3	4	5	6	m ± SEM	*P* Value
Control									
Cumulative dose (mg/kg)		0.29	0.36	0.20	0.29	0.26	0.32	0.29 ± 0.02	
Preseizure MUA level	(%)	100	100	100	100	100	100	100	
MUA increase by seizure	(%)	100	100	100	100	100	100	100	
Duration of seizure	(s)	47	32	28	40	35	38	36.7 ± 3.0	
	(%)	100	100	100	100	100	100	100	
1.5% Enflurane									
Cumulative dose (mg/kg)		0.40	0.34	0.38	0.42	0.36	0.49	0.40 ± 0.02	*
Preseizure MUA level	(%)	50	39	94	50	45	60	56.3 ± 8.8	†
MUA increase by seizure	(%)	64	63	73	70	65	68	67.2 ± 1.7	†
Duration of seizure	(%)	70	78	71	70	65	68	70.3 ± 1.9	†
3.5% Enflurane									
Cumulative dose (mg/kg)		0.33	0.32	0.28	0.36	0.32	0.40	0.34 ± 0.02	‡
Preseizure MUA level	(%)	25	26	38	27	28	30	29.0 ± 2.1	†§
MUA increase by seizure	(%)	41	43	64	42	40	46	46.0 ± 4.1	†¶
Duration of seizure	(%)	19	31	54	25	26	40	32.5 ± 5.7	†¶

* $P < 0.01$ *versus* control.
† $P < 0.001$ *versus* control.
‡ $P < 0.05$ *versus* 1.5% enflurane.
§ $P < 0.01$ *versus* 1.5% enflurane.
¶ $P < 0.001$ *versus* 1.5% enflurane.

seizure, except in one cat given diazepam. Here, the CNS electrical activities showed identical patterns to those induced by enflurane: the frequency of focal spikes increased and the level of background reticular multiunit activity decreased considerably.

Discussion

Our recent study[21] in cats indicated that the convulsant property of enflurane was biphasic: the maximum effect was in between 3 and 4%, whereas the effects were significantly less potent both above or below this range. Since we intended to prove a rather paradoxic hypothesis that a convulsant anesthetic had an anticonvulsant property, the drug action was examined with the concentration of maximum convulsive property in the present study. Utilizing several epilepsy models (see McNamara[22] and Woodbury,[23] for other models), we found that enflurane had a potent anticonvulsant action, not only in the subconvulsive but also in the convulsive concentrations. The pattern of anticonvulsive action, however, was dissimilar when compared with different experimental models. The suppression of penicillin-induced cortical focal seizure was dose dependent, but suppressions in amygdaloid kindled and bicuculline models were biphasic, in that the anticonvulsive actions of subconvulsive dose were more extensive. Thus, enflurane seems to have both convulsive and anticonvulsive properties, both of which are dose-dependent in the range examined (to 3.5%): in light anesthesia, the balance was in the dominance of anticonvulsant action and the induction of seizure was more difficult, while in case of deep anesthesia, the dominance was in the convulsant action; seizures could be induced more readily but the intensity of convulsion was suppressed by the anticonvulsant action in both electrographic and behavioral expressions. The anticonvulsant action or the action to increase the convulsive threshold may relate to the nonspecific CNS suppressive actions reported previously.[10–12]

The blockade of sustained seizure in penicillin-induced status epilepticus was associated with an increase in frequency of interictal spike discharges; the same effect was confirmed with diazepam and thiamylal, widely used anticonvulsants; and the possibility of potentiation by enflurane of the penicillin-induced focal activity was ruled out.

The facilitation by a convulsive dose of enflurane of remote propagation of amygdaloid after-discharge seen in the present study is also intricate. The enflurane-induced convulsion is related to afferent systems, such as somatosensory[24] or auditory[6,11] systems belonging to the neocortical system, while the amygdaloid nucleus is

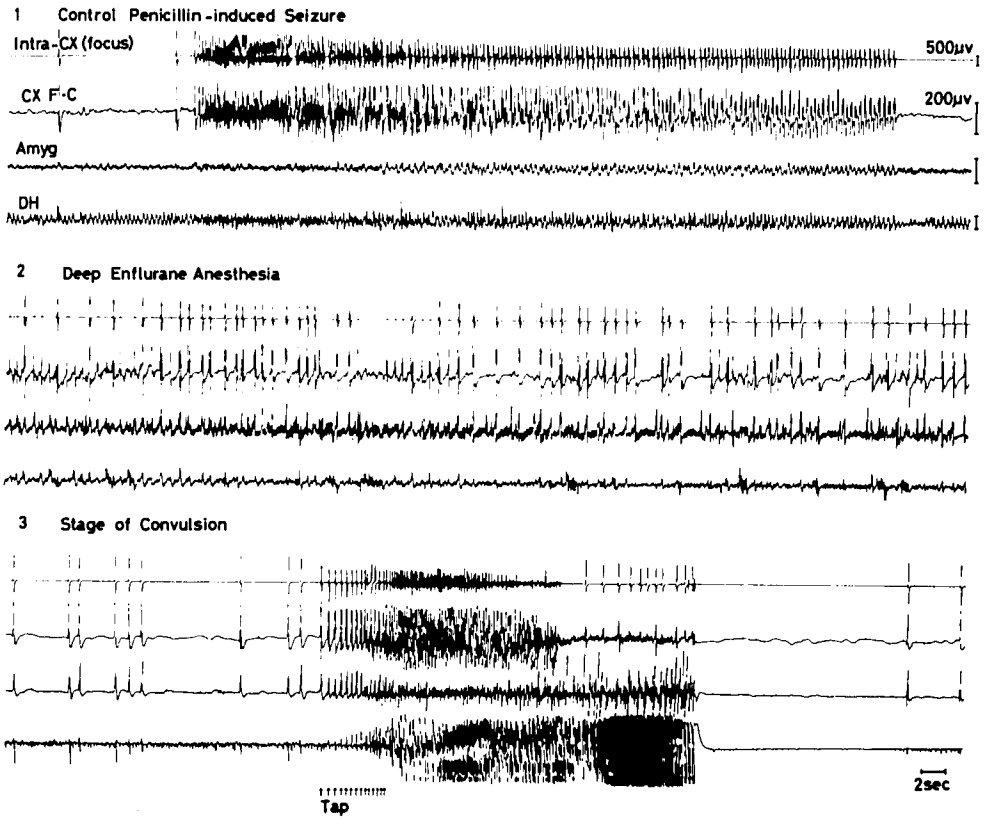

FIG. 7. Enflurane actions on the penicillin-induced cortical focal seizure. Intra-CX (focus) = intracortical recording of epileptic focus; CX F-C = cortical EEG recorded with frontocentral lead. The traces of both deep enflurane anesthesia and stage of convulsion were obtained during administration of 3.5% enflurane, and the numbers 1–3 correspond to those in figure 8. Sustained seizure was completely blocked by enflurane (deep anesthesia), while somatic stimulation by tapping the body induced generalized seizure (stage of convulsion).

related to the olfactory sensation and belongs to the class of paleocortical system or limbic structure. Olfactory stimulus-induced convulsion during enflurane anesthesia has apparently not been documented. Although deep enflurane anesthesia definitely suppressed the excitability of the amygdaloid kindled focus in that the threshold current required to induce seizure was increased significantly, it simultaneously induced a state ripe for the development of seizure in the nonfocal area of the brain tissue. Once the amygdaloid after-discharge induced by stimulation with a suprathreshold current propagated to involve the neural route responsible for the propa-

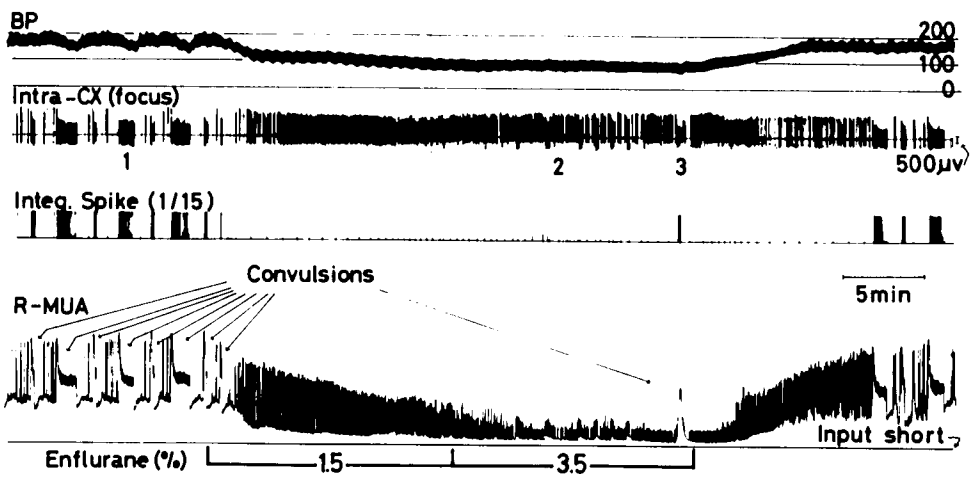

FIG. 8. Enflurane actions on penicillin-induced focal seizure. BP = arterial blood pressure; Integ. Spike (1/15) = spike counter indicating 15 spikes/1 signal; Convulsions = sustained seizure. The numbers below the trace of intracortical EEG correspond to those of figure 7. Before administration of enflurane, there were repeated appearances of sustained seizure, indicating status epilepticus. These seizures were blocked by enflurane, 1.5%. The sustained seizure appearing near the end of administrating 3.5% enflurane was induced by tapping, indicating that the stage of anesthesia is in that of convulsion. The status epilepticus reappeared after discontinuation of enflurane anesthesia.

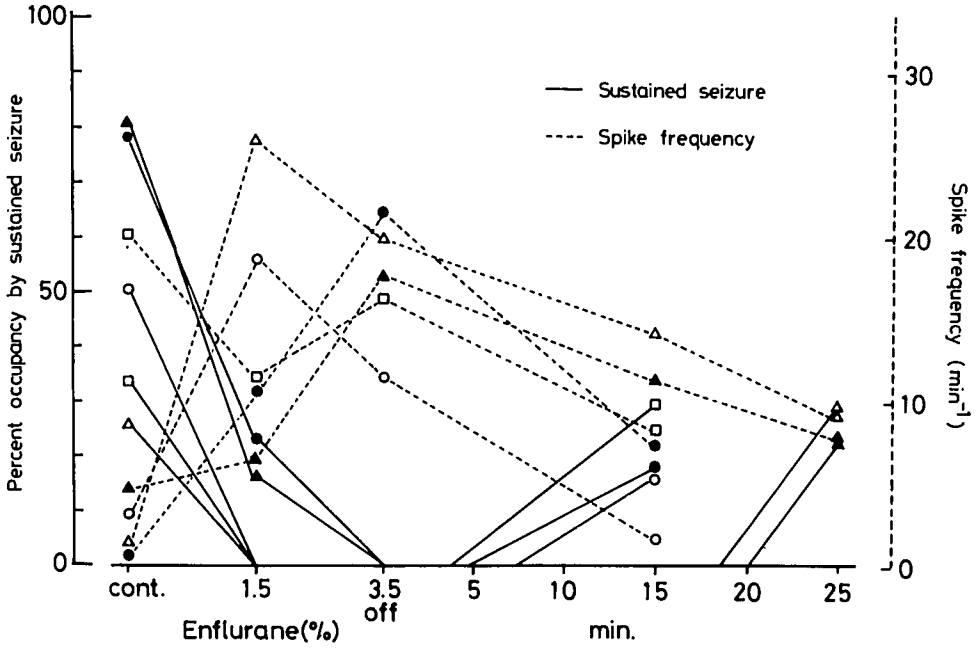

FIG. 9. Changes of per cent occupancy of EEG by sustained seizure and frequency of spike in five cats. The solid lines represent per cent occupancy by sustained seizure and the broken lines the frequency of spike. The enflurane actions are represented by the peak values, and the recovery phase is shown by the time course. The sustained seizure was blocked completely by 3.5% enflurane, while the frequency of spike increased.

gation of enflurane-induced seizure, it involved the whole brain tissue instantaneously. This resulted in maximum CNS stimulation in the electrographic and behavioral expressions at the early phase of ictus (see figs. 5 and 7 in the present study and fig. 9 of Mori[11]), and the facilitation of remote propagation ensued.

The neural bases of the convulsant actions of penicillin and bicuculline and those of the anticonvulsant actions of barbiturates and diazepam have been attributed to their actions on the GABAergic receptor complex: a blockade for convulsant and a facilitation for anticonvulsant actions of GABA-mediated postsynaptic responses have been postulated.[23,25,26] Triner *et al.*[13] postulated the role of cerebellar cyclic GMP content in suppressing GABA-blocker-induced convulsions by enflurane in mice. However, their study was restricted to the range of subconvulsive concentrations of enflurane. As suggested in the case of phenytoin,[27] a drug that decreases cyclic GMP content and possesses potent anticonvulsant actions, the possibility that these two phenomena are not related directly cannot be ruled out. The present findings that the action of a convulsive dose of enflurane was not additive but rather suppressive to the convulsive action of penicillin and bicuculline suggest that this action of enflurane is exerted through a mechanism other than those directly related to the GABA-receptor complex.

Epilepsy is a collective designation for a group of CNS disorders having in common the occurrence of sudden and transitory episodes of abnormal phenomena of motor, sensory, autonomic, or psychotic origin. It is generally agreed[28] that an accurate evaluation of the type of seizure is essential for the rational pharmacology of epilepsy, and improper diagnosis of the type of seizure is considered as one of the common causes of failure of antiepileptic medication, since the pharmacology is selective for a particular type of seizure. Extrapolation of findings obtained through experimental models to all types of epilepsy is to be avoided. Of particular consideration is the case of certain myoclonic type epilepsies, such as progressive myoclonic epilepsy and photosensitive epilepsy, in which components of sensory evoked potentials are markedly enhanced,[29-31] as in the case of enflurane anesthesia. The actions of enflurane on this type of epilepsy have apparently not been documented.

As proposed by Jackson,§ generalized convulsions result from invasion of the whole brain tissue by focal excessive discharges. Not the appearance of spikes in the EEG of the motor cortex but rather the involvement by seizure of the brain stem reticular neurons, assessed by the multi-unit recording method, is reportedly essential for the appearance of myoclonic jerking of an epileptic character.[20,32] In the present study, in accordance with suppression of the background reticular neuronal activity, the activation by seizure of the brain stem reticular neuronal firing was suppressed by both subconvulsive and convulsive concentrations of enflurane, in the case of bicuculline and amygdaloid stimula-

§ Cited from Rall and Schleifer.[28]

tion-induced seizures, and these suppressions were associated with suppression of convulsive movements, observed visually. Thus, the severity of convulsion due to the patient's pathology, if occurring during enflurane anesthesia, should also be markedly suppressed in comparison with that occurring in a nonanesthetized state.

Our observations support the postulations of Gallagher *et al.*[15] and Lebowitz *et al.*,[16] who suggested that mechanisms related to the convulsive action of enflurane differ from those of epileptic focal activity in humans. We conclude that there is little, if any, possibility that enflurane exacerbates the preexisting epileptic foci, but it does suppress both the excitability of epileptic foci *per se* and the severity of convulsion and can be used safely in the anesthetic practice of epileptic patients.

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