Laboratory Investigations

The divergent actions of volatile anaesthetics on background neuronal activity and reactive capability in the central nervous system in cats

Takashi Ogawa MD, Koh Shingu MD,
Masatoshi Shibata MD, Masami Osawa MD,
Kenjiro Mori MD, FCAnaes

The effects of halothane, isoflurane, and enflurane on background neuronal activity and reactive capability in the central nervous system were studied in cats. The background neuronal activity was assessed by midbrain reticular cell firing, which was measured by the method of multi-unit activity, and the EEG in the cortex, amygdala, and hippocampus. The reactive capability was assessed by evoked responses in the visual neuronal pathway. All anaesthetics studied suppressed reticular cell firing in a dose-dependent manner, and the suppression by halothane (43.8 ± 10.3% of control, mean ± SD) was less than isoflurane (66.5 ± 5.8%, $P < 0.01$) and enflurane (73.1 ± 8.8%, $P < 0.05$) at 1 MAC. Spontaneous EEG spikes developed at 4.8% isoflurane and 3.6% enflurane anaesthesia. Phasic activation of reticular cell firing was associated with EEG spikes during isoflurane and enflurane anaesthesia, and the activation during enflurane anaesthesia was greater than during isoflurane anaesthesia ($P < 0.01$). Photic stimulation provoked EEG spikes and repetitive stimulation induced seizure activity only at 3.6% enflurane anaesthesia. Halothane and isoflurane suppressed stimulation induced responses in the visual neuronal pathway. The amplitudes of N_1 in visual cortical evoked responses induced by photic stimulation were suppressed to 70.1 ± 24.5% of control at 2.4% halothane and 39.3 ± 27.3% at 4.8% isoflurane. Enflurane, at 3.6%, augmented the evoked response induced by photic stimulation (398.4 ± 83.0% of control in the amplitude of N_1). These results indicate that all the agents studied had suppressive actions on background neuronal activity in the order halothane < isoflurane = enflurane. The effects on reactive capability were divergent among agents, e.g., enflurane enhanced, halothane suppressed, and the actions of isoflurane were intermediate. We conclude that the anaesthetic effects on background activity and on reactive capability are divergent and that suppression of reactive capability is a factor in determining the ease of clinical application of the anaesthetics.

L'étude porte sur les effets de l'halothane, l'isoflurane et de l'enflurane sur l'activité neuronale de fond et la capacité réactive du système nerveux central chez le chat. L'activité neuronale de fond est mesurée par la décharge des cellules réticulaires mésencéphaliques, elle-même par la méthode de l'activité multi-unitaire et l'EEG cortical, amygdalien et hippocampique. La capacité réactive est évaluée les réponses évoquées sur la voie de conduction visuelle neuronale. Tous les

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From the Department of Anesthesia, Kyoto University Hospital, Sakyo-ku, Kyoto 606, Japan.

Address correspondence to: Dr. K. Mori, Department of Anesthesia, Kyoto University Hospital, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606, Japan.

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anesthésiques suppriment la décharge de la cellule réticulaire proportionnellement à la concentration. La suppression par l'halothane (43,8 ± 10,3% du contrôle, moyenne ±E.T.) a été moindre que par l'isoflurane (66,5 ± 5,8%, P < 0,01) et l'enflurane (73,1 ± 8,8%, P < 0,01) à 1 MAC. Des pointes spontanées sont apparues avec l'anesthésie à l'isoflurane 4,8% et à l'enflurane 3,6%. L'activation phasique de la décharge de la cellule réticulaire est associée à des pointes EEG pendant l'anesthésie à l'isoflurane et à l'enflurane, et l'activation pendant l'enflurane est plus grande que pendant l'isoflurane (P < 0,01). La stimulation photique entraîne des pointes EEG et une stimulation répétée provoque de l'activité épileptique à seulement 3,6% d'enflurane. L'halothane et l'isoflurane suppriment les réponses évoquées induites par stimulation dans la voie de transmission neuronale visuelle. Les amplitudes de N_1 pour les réponses évoquées induites au cortex visuel par stimulation photique sont supprimées à 70,1 ± 24,5% du contrôle avec halothane 2,4% et à 39,3 ± 27,3% avec l'isoflurane 4,8%. L'enflurane à 3,6% augmente la réponse évoquée induite par stimulation photique (398,4 ± 83,0 du contrôle dans l'amplitude de N_1). Ces résultats indiquent que tous les agents étudiés ont une action suppressive sur l'activité neuronale de fond dans l'ordre halothane < isoflurane = halothane. Les effets sur la capacité réactive divergent parmi les agents, c'est-à-dire que l'enflurane l'augmente, l'halothane la supprime et l'isoflurane occupe une place intermédiaire. Nous en concluons que les effets anesthésiques sur l'activité de fond et la capacité réactive divergent et que la suppression de la capacité réactive est un facteur déterminant sur la facilité de l'utilisation des anesthésiques en clinique.

Enflurane is not a sufficiently potent anaesthetic to suppress motor responses to surgical stimulation, and supplementation with muscle relaxants or nitrous oxide is usually required. In humans, when the inspired enflurane concentration is increased to obtain better muscular relaxation, the motor response is not necessarily depressed but may be facilitated and an epileptoid state, characterized by muscular twitch, is induced. Laboratory animal studies indicated that deep levels of enflurane anaesthesia did not produce total brain suppression but a sensory stimulation-induced epileptoid state: sensory stimulation induced EEG spikes which were associated with myoclonic jerking, and repetitive stimulation induced generalized tonic-clonic convulsions.[1] It is generally agreed that the potency of anaesthetics correlates with their lipid solubility and that the product of the partial pressure required to induce anaesthesia and the oil/gas partition coefficient varies little for a given animal.[2] Koblin[2] pointed out that some deviation from this correlate does exist with the convulsant anaesthetics, such as flurothyl, compound 485 and enflurane, and postulated that the convulsant property of anaesthetics opposed the hypnotic properties and increased anaesthetic requirement. Two types of CNS electrical activity can be recorded and assessed: "spontaneous" or "background" activity and evoked activity, which is a response to stimulation. Background activity is that recorded when there is minimal afferent input and is tonic in nature. Evoked activity induced by external stimulation is linked with the stimulus and is phasic in nature. It was assumed that the action of the anaesthetic agents on background reticular cell firing was an index of hypnotic action and that the sensory evoked response was an index of suppression of reactive capability to surgical stimulations. The present study compared the convulsant and CNS depressant actions of halothane, isoflurane, and enflurane by assessing the effects on visual evoked response and the background reticular cell firing.

Methods

Eleven cats of either sex weighing 2.5–4.0 kg were used in the study, which was approved by the Institutional Committee on Animal Research. The anaesthetic agents studied were halothane, isoflurane, and enflurane, and each agent was administered to five cats at one week intervals.

Placement of electrodes

Cats were anaesthetized with pentobarbital 40 mg · kg^{-1} *ip* for the placement of electrodes. The animals were placed on a stereotaxic apparatus. Seven electrodes were inserted and fixed according to the atlas by Snider and Niemer[3] as follows: skull above the visual cortex (A:-6, L:3) and frontal sinus, midbrain reticular formation (A:2, L:3, D:-2), dorsal hippocampus (A:2, L:8, D:9), amygdala (A:12, L8, D:-6), optic chiasma (A:14.5, L:0.5, D:-5), and optic radiation (A:5.5, L:7.5, D:8). The electrodes placed in the skull were made of stainless steel screws 2 mm in diameter, and the electrodes placed in the subcortical structures were made of two stainless steel wires, 0.2 mm in diameter, in parallel, and insulated with epoxyresin except tips. The distance between the tips was 0.5–1.0 mm. For the placement of electrodes in the optic chiasma, the response to photic stimulation from the electrode was recorded while advancing the electrode, and the optimum position was the site where the biggest response was obtained. For placement of electrodes in the optic radiation, the response in the visual cortex to stimulation of the electrode was recorded while it was advanced.

Administration of anaesthetics

Control values for EEG, multi-unit activity (MUA), evoked responses were obtained under non-anaesthetized states more than two weeks after the placement of electrodes. Cats were anaesthetized with 3% halothane, 4% isoflurane, or 4% enflurane in oxygen, and their tracheas

were intubated after intravenous administration of alcuronium 0.1 mg. Then, the inspired concentration of anaesthetic was decreased.

Anaesthetics were administered using a calibrated vaporizer (Cyprane). The inspired concentrations studied were 0.4, 1.2, and 2.4% of halothane, 0.8, 2.4, and 4.8% of isoflurane, and 0.6, 1.8, and 3.6% of enflurane. The inspired concentrations were increased at intervals of 30 min. The end-tidal gas was sampled, and EEG, evoked potentials, and MUA were recorded at the end of each step. The concentrations of anaesthetics of the gas samples were measured by gas chromatography (Shimazu GC 6AM). The lungs were ventilated using a Harvard pump at an initial tidal volume of 13 $ml \cdot kg^{-1}$ and at a rate of 20 min^{-1}. The settings were adjusted to maintain the end-tidal PCO_2 at 30–34 mmHg measured by infrared CO_2 analyzer (Cabitron RN-20N). Rectal temperature was maintained at 36.5–38.5° C by applying heated water mattress.

EEG recording

Electroencephalographs from the visual cortex, dorsal hippocampus, and amygdala were recorded on an eight channel polygraph (Sanei Recti-Horiz-8K). The frontal sinus electrode was used as the reference for recording EEG from the cortex. The other EEGs were recorded with the bipolar manners between the two active points of the electrodes placed in the subcortical structures. The time constant was set at 0.1 sec and the filter at 100 cps. Recording paper speed was 10 $mm \cdot s^{-1}$.

Recording evoked response

The visual cortex responses to photic stimulation and electrical stimulation of the optic chiasma and optic radiation were recorded. Photic stimulation was carried out with an electric flash apparatus (Nihonkoden MS-2PS), placed at a distance of 10 cm from the cornea. The electric stimuli were suprathreshold in voltage, 0.1 ms in duration, and rectangular in shape. The intervals between stimulations were 1–3 sec and were controlled manually. The frontal sinus electrode was used as the reference for recording evoked potentials. The recording conditions of the evoked response were the same as those during recording of the EEG, except that the filter was set at "off." Ten responses were summated and averaged by a signal processor (Sanei 7S06A), and were recorded on an X-Y plotter (Watanabe WX44Z). The peak latencies and amplitudes of the waves were measured and the changes induced by anaesthetics were expressed as a percentage of the control, mean ± SD.

Midbrain reticular formation multi-unit activity

Neuronal firing in midbrain reticular formation was measured by the method of multi-unit activity (MUA)[4] and was recorded on a slow moving paper recorder (Sanei Rectigraph 8K) with the paper speed of 5 $mm \cdot min^{-1}$. It was obtained differentially between the two active points of electrodes, amplified (Sanei 1205C) and then sent to a high-pass filter. This high frequency activity was rectified and smoothed with an electronic circuit (envelop detector) with a smoothing time constant of 50 msec and was expressed by the oscillation of DC voltage: the higher the DC level, the greater the firing of a population of units. The noise level of the recording system was estimated with the DC level obtained by inserting a 10 KΩ resistor and a short across the input in place of the animal. The MUA level was measured as the height from the short line to the lower limit of the multiunit tracing. The signal to noise ratio exceeded 10 in all cases. The values obtained during the non-anaesthetized state served as control and the changes induced by anaesthetics were expressed as a percentage of control, mean ± SD.

Spike and seizure provoking test

The ability of photic stimuli or electric stimulation of the optic chiasma or optic radiation to provoke a spike and seizure activity in EEG was studied. The stimulating conditions were the same as those described in the section of recording evoked responses.

Multi-unit activity and photic stimulation-induced response in optic chiasma and optic radiation

Multi-unit activity response and evoked potentials, induced by photic stimulation, in the optic chiasma and optic radiation were obtained in two cats with each anaesthetic agent. The frontal sinus electrode was used as a reference in recording evoked potentials. Multi-unit activity and evoked potentials were displayed on a cathode ray oscilloscope (Nihonkoden VC7) with the sweep speed of 100 $ms \cdot cm^{-1}$ and were photographed with a Polaroid camera.

Statistics

The end-tidal concentrations of the agents were corrected to MAC values, and the MUA levels at 1 MAC of each cat were obtained by interpolation. The MAC values used were 1.2% for halothane, 1.6% for isoflurane, and 2.4% for enflurane.[5] The MUA levels, the peak latencies and amplitudes of evoked potentials were compared with the control values by repeated measures analysis of variance and paired t test with Bonferroni's correction. The enhancements of MUA associated with EEG spikes were compared between isoflurane and enflurane using the unpaired t test. Probability values <0.05 were considered to be statistically significant.

TABLE I End-tidal concentrations of anaesthetics and changes in reticular multi-unit activity (RF-MUA) level ($n = 5$, mean ± SD)

	Inspired conc.	*End-tidal/inspired ratio*	*End-tidal Conc. (MAC)*	*RF-MUA levels**
Halothane	0.4%	0.55 ± 0.05	0.18 ± 0.02	89.9 ± 9.2
	1.2%	0.62 ± 0.05	0.62 ± 0.05	75.8 ± 6.9†
	2.4%	0.66 ± 0.08	1.33 ± 0.15	42.9 ± 11.9‡
Isoflurane	0.8%	0.72 ± 0.07	0.36 ± 0.03	65.7 ± 8.0‡
	2.4%	0.74 ± 0.06	1.11 ± 0.08	27.1 ± 10.2‡
	4.8%	0.73 ± 0.05	2.24 ± 0.16	19.1 ± 5.9‡
Enflurane	0.6%	0.62 ± 0.07	0.15 ± 0.02	74.0 ± 13.7†
	1.8%	0.66 ± 0.06	0.50 ± 0.05	57.4 ± 3.1‡
	3.6%	0.69 ± 0.05	1.03 ± 0.07	23.9 ± 12.6‡

*% changes of control. †$P < 0.05$ versus control. ‡$P < 0.01$ versus control.

Results

End-tidal concentrations of anaesthetics

The end-tidal concentrations at each step are shown in Table I.

EEG

The EEG patterns at different concentrations for each agent are shown in Figure 1. At 0.4% halothane, spindles occurred at 12–15 Hz, similar to barbiturate spindles, developed in one cat of the five. The amplitude increased and the frequency decreased with higher concentrations, e.g., dominant cortical EEG activities changed from 10–12 Hz 50 μV at control to 2–3 Hz 250 μV at 2.4% halothane. During isoflurane anaesthesia, spike burst and suppression patterns developed with 2.4% and the suppression periods gradually became dominant, and the cortical EEG became almost electrically silent. However, increasing recording sensitivity showed very low amplitude rhythmic waves, 6–8 Hz 6–10 μV, in the cortex, which synchronized with 30–40 μV waves in the hippocampus. Sporadic spikes occurred in the amygdala before the development of cortical electric silence. Spikes developed in the cortex and their amplitude increased with time during 4.8% isoflurane. With enflurane anaesthesia, high-amplitude slow waves were dominant at 1.8%. Spikes appeared at first at the amygdala and spread to the hippocampus and cortex, the amplitude and occurrence of spikes increased with time and the background waves were suppressed in amplitude and became isoelectric at 3.6% enflurane. Although spikes developed at 4.8% isoflurane and at 3.6% enflurane, the characteristics of spikes seemed to be different between agents, e.g., cortical spikes occurred during enflurane anaesthesia and synchronized with those in amygdala and hippocampus, but cortical spikes during isoflurane anaesthesia did not always synchronize with those in other subcortical structures.

Midbrain reticular formation multi-unit activity

All agents suppressed midbrain reticular formation MUA in a dose-dependent manner (Table I and Figure 2). The MUA levels at 1 MAC were 56.2 ± 10.3% with halothane, 33.5 ± 5.8% with isoflurane, and 26.9 ± 8.8% with enflurane. Suppression by halothane was less than that by isoflurane ($P < 0.01$) and enflurane ($P < 0.05$). Phasic enhancement of multi-unit activity in the midbrain reticular formation occurred synchronously with EEG spikes during 4.8% isoflurane and 3.6% enflurane anaesthesia. The enhancement with EEG spikes was larger during enflurane (33.4 ± 7.1%) than during isoflurane anaesthesia (10.3 ± 5.3%, $P < 0.01$).

Spike and seizure provoking test

Photic stimulation provoked an EEG spike, and repetitive ($1.5\ s^{-1}$) photic stimulation induced seizure activities in the EEG during 3.6% enflurane. Midbrain reticular formation MUA enhanced markedly during seizure (Figure 3). Photic stimulation during deep enflurane anaesthesia was the only condition which provoked a spike or seizure in the EEG. Subcortical electrical stimulation, by other agents, or lower concentrations of enflurane did not provoke spikes or seizure (Figure 4 for photic stimulation at 4.8% isoflurane).

Evoked response in visual cortex

PHOTIC STIMULATION

Photic stimulation induced tetraphasic responses in the visual cortex consisting of positive-negative-positive-negative (P_1, N_1, P_2, N_2) deflections (Figure 5). The mean

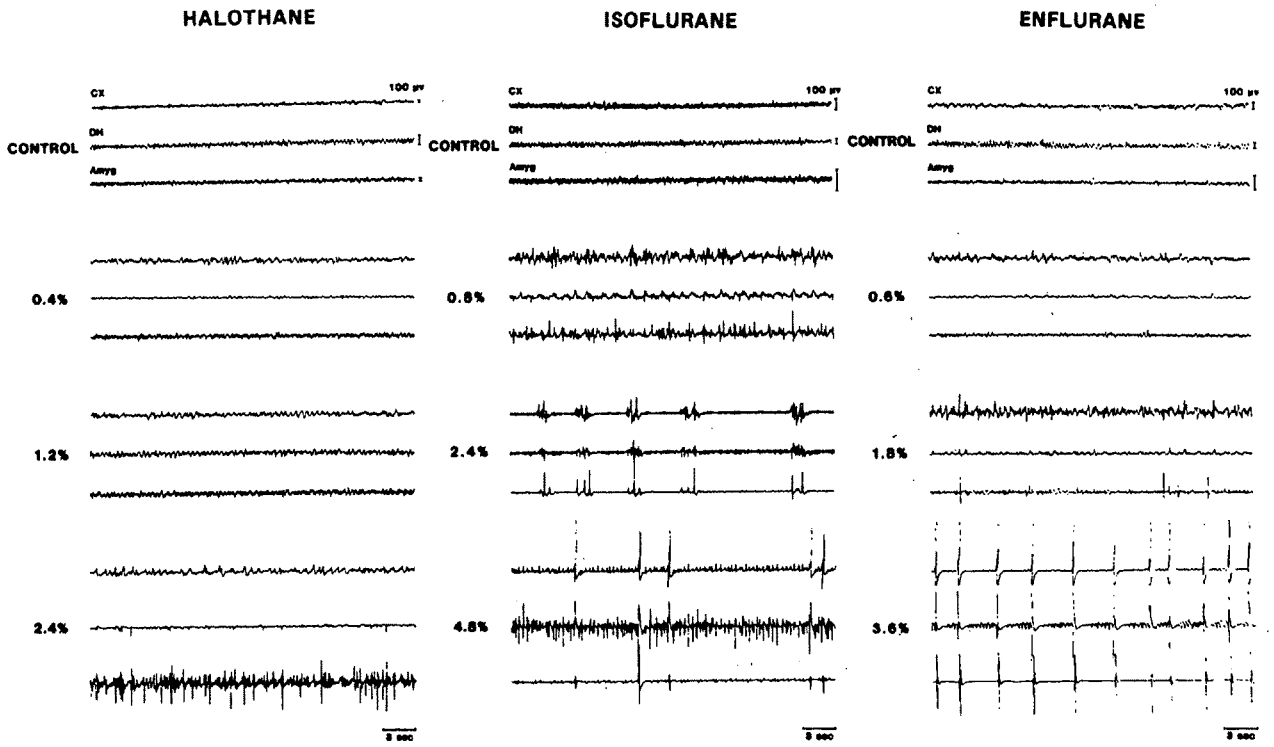

FIGURE 1 The EEG changes in cortex, dorsal hippocampus, and amygdala produced by halothane, isoflurane, or enflurane. CX: visual cortex, DH: dorsal hippocampus, and Amyg: amygdala. With higher concentrations of halothane, the amplitude of cortical EEG increased and the frequency decreased. During isoflurane anaesthesia, the amplitude of cortical EEG increased and the frequency decreased at 0.8%. At 2.4%, spike burst and suppression patterns developed in the cortex, hippocampus and amygdala. At 4.8%, sporadic spikes occurred in the cortex, hippocampus and amygdala. The basal activities in the cortex were low amplitude rhythmic waves, which were synchronous with waves in the hippocampus. During enflurane anaesthesia, the amplitude of cortical EEG increased and the frequency decreased with higher concentrations. At 3.6%, sporadic spikes occurred in the cortex, hippocampus and amygdala. The background waves were almost flat in the cortex.

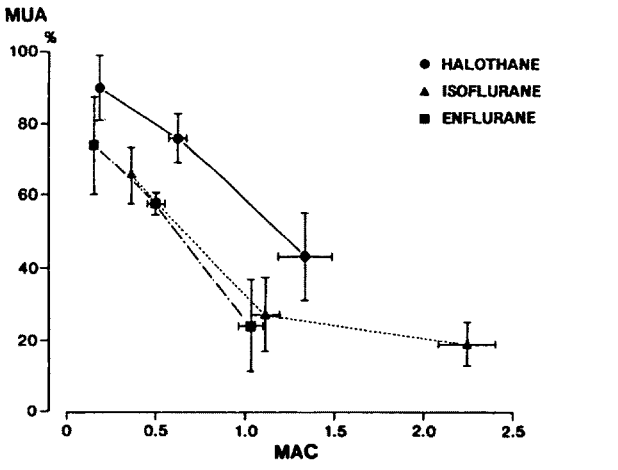

FIGURE 2 The effects of halothane, isoflurane, and enflurane on multi-unit activity (MUA) in midbrain reticular formation. All agents suppressed MUA in a dose-dependent manner: the suppression by halothane was less than by isoflurane and enflurane at equivalent MAC concentrations (mean ± SD).

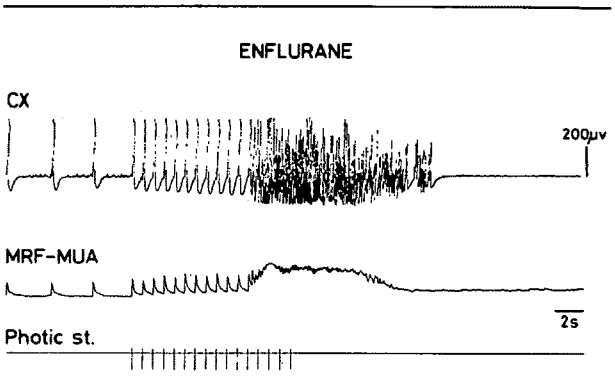

FIGURE 3 Photic-evoked seizure activities during 3.6% enflurane anaesthesia. CX: visual cortex, MRF-MUA: multi-unit activity in the midbrain reticular formation, Photic st.: markers of photic stimulations. Spontaneous spikes, synchronous with enhancement of MUA, appeared in cortical EEG. The repetitive (1.5 c/s) photic stimulations provoked spikes in the cortical EEG and increases of MUA, and seizure activities developed.

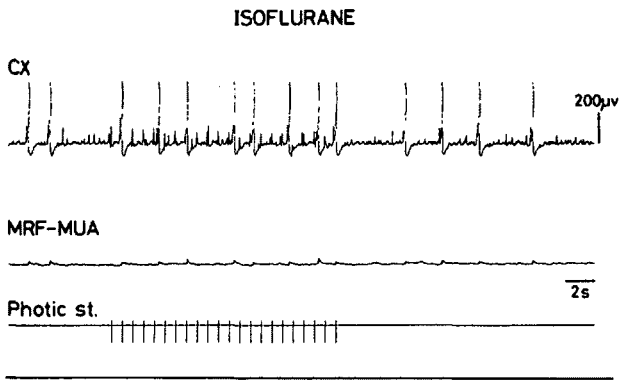

FIGURE 4 The effect of photic stimulation during 4.8% isoflurane anaesthesia. CX: visual cortex, MRF-MUA: multi-unit activity in the midbrain reticular formation, Photic st.: markers of photic stimulations. Sporadic spikes in the cortical EEG and the concomitant small increase of MUA are shown. Photic stimulation induced small spike waves in the cortical EEG, but induced no enhancement of MUA. Sporadic spikes are shown, but are not associated with the photic stimulation.

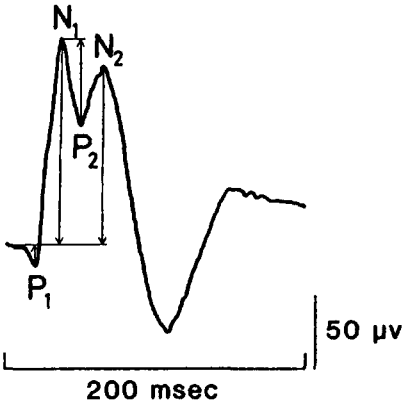

FIGURE 5 Photic stimulation induced positive-negative-positive-negative responses in the visual cortex. The respective deflections were named P_1, N_1, P_2 and N_2. The methods of measurements of amplitudes of the deflections are shown in the figure.

latent periods of the peaks of deflections were 18.7 ms for P_1, 39.5 ms for N_1, 51.4 ms for P_2, and 65.4 ms for N_1. The P_1 was a small deflection and was suppressed by anaesthesia. It was difficult to measure its latency and amplitude in some cases, but then the latency and the amplitude of N_1, P_2, and N_2 were measured. The peak latencies were prolonged by halothane in a dose-dependent manner (Table II). Although the amplitudes of N_1 and N_2 were suppressed by halothane, the suppression was not dose-dependent, whereas isoflurane suppressed the amplitudes in a dose-dependent manner (Table II). Prolongation of the peak latencies by isoflurane was not dose-dependent. Enflurane at 0.6 or 1.8% had no effect on the evoked response, but 3.6% enflurane prolonged the peak latency and increased the amplitude markedly (Table II, Figure 6).

ELECTRICAL STIMULATION OF THE OPTIC CHIASMA

Electrical stimulation of the optic chiasma induced four positive waves which were followed by a negative wave in the visual cortex (Figure 7). All anaesthetics prolonged the peak latencies and suppressed the amplitudes (Table III and IV).

ELECTRICAL STIMULATION OF THE OPTIC RADIATION

Electrical stimulation of the optic radiation induced four positive and a negative wave similar to the response to stimulation of optic chiasma, but the peak latencies were about 1 msec shorter than those of the response to stimulation of optic chiasma (Figure 8). All anaesthetics pro-

TABLE II Effects of anaesthetics on the cortical evoked response induced by photic stimulation (n = 5,% of control, mean ± SD)

		N1		*P2*		*N2*	
Agent	*Inspired conc.*	*Amplitude*	*Latency*	*Amplitude*	*Latency*	*Amplitude*	*Latency*
Halothane	0.4%	78.7 ± 28.3	107.2 ± 9.0	139.7 ± 79.7	106.2 ± 5.3	61.6 ± 6.0*	120.4 ± 13.2*
	1.2%	52.6 ± 11.2†	103.2 ± 10.3	138.1 ± 85.0	118.9 ± 25.1	30.9 ± 13.2†	124.4 ± 12.6†
	2.4%	70.1 ± 24.5	132.7 ± 18.3†	149.0 ± 165.5	165.2 ± 31.8†	35.6 ± 26.7†	158.4 ± 6.5†
Isoflurane	0.8%	91.2 ± 19.2	108.4 ± 8.3	130.4 ± 84.0	150.7 ± 83.0	72.8 ± 27.2	107.4 ± 9.2
	2.4%	48.4 ± 27.1†	211.8 ± 55.5†	97.3 ± 70.7	220.2 ± 55.1	43.0 ± 29.5†	220.5 ± 30.1
	4.8%	39.3 ± 27.3†	103.1 ± 5.4	84.9 ± 84.7	136.5 ± 9.7	5.5 ± 7.6	116.9 ± 24.7
Enflurane	0.6%	94.9 ± 13.6	113.8 ± 15.5	98.6 ± 33.2	125.0 ± 25.1	77.4 ± 20.9	118.5 ± 13.9
	1.8%	105.2 ± 34.0	95.1 ± 5.3	195.1 ± 105.0	111.5 ± 28.4	92.7 ± 46.2	108.8 ± 17.5
	3.6%	398.4 ± 83.6†	133.0 ± 19.2*	373.6 ± 276.8	123.5 ± 14.2	453.8 ± 229.0†	115.1 ± 19.7

*$P < 0.05$ versus control. †$P < 0.01$ versus control. 4.8% isoflurane depressed P2 and N2 amplitude and these waves could not be detected in three animals. Statistical analysis could not be carried out in these.

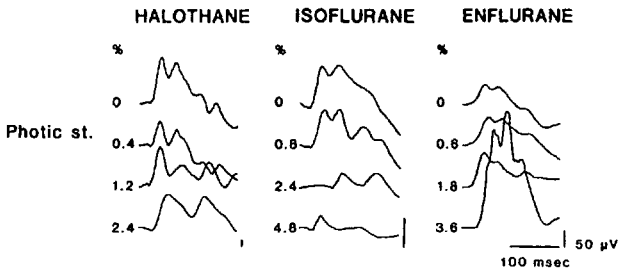

FIGURE 6 The effects of anaesthetics on the cortical response to the photic stimulation. Halothane and isoflurane depressed the response, but 3.6% enflurane augmented the response. The peak latency was prolonged by all agents except 4.8% isoflurane, which shortened the peak latency.

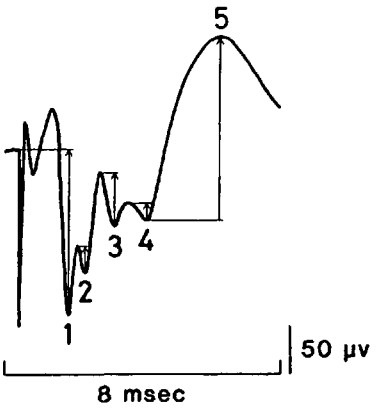

FIGURE 7 Cortical response to the electrical stimulation of the optic chiasma. The response consists of 4 positive (1–4) waves and a negative wave (5) following a positive deflection. The first big positive wave is the electrical stimulation which is seen through volume conductance. The methods of measurements of the amplitude of the waves are shown in the figure.

longed the peak latencies and suppressed the amplitudes of the response (Tables V and VI). The suppression by anaesthetics of the evoked response induced by optic radiation stimulation was less than that induced by optic chiasma stimulation with all the agents studied.

Multi-unit activity and evoked potential in optic chiasma induced by photic stimulation

The spontaneous MUA in the optic chiasma was suppressed by all anaesthetic agents in a dose-related manner (Figure 9). Multi-unit activity responses to photic stimulation were depressed by all agents. The latency of the response was markedly delayed at 2.4% isoflurane, but recovered to that of the control at 4.8% isoflurane. The evoked potential in the optic chiasma induced by photic stimulation consisted of a large positive and successive small negative components. The amplitudes of evoked potential were depressed by halothane and isoflurane. The latency of evoked potential was prolonged markedly at 2.4% isoflurane, but recovered to that of control at the highest concentration. The evoked potential at 3.6% enflurane showed a large negative component.

Multi-unit activity and evoked potential in optic radiation induced by photic stimulation

The spontaneous MUA in the optic radiation was suppressed by all agents (Figure 10). Multi-unit activity responses to photic stimulation were suppressed by halothane and isoflurane. The MUA response was enhanced at 3.6% enflurane. The evoked potential in the optic radiation induced by photic stimulation consisted of a small positive and large negative components. The evoked potential was depressed by halothane and isoflurane. The depression by isoflurane was greater than that by halothane. The amplitude of evoked potential of the

TABLE III Effects of anaesthetics on the amplitude of cortical evoked response induced by electric optic chiasma stimulation (n = 5,% of control, mean ± SD)

Agent	Inspired conc.	Component 1	2	3	4	5
Halothane	0.4%	73.8 ± 11.2†	100.0 ± 35.0	88.1 ± 35.2	27.1 ± 21.2†	54.7 ± 21.1†
	1.2%	53.3 ± 6.6†	55.7 ± 16.6*	43.4 ± 22.7†	14.1 ± 14.7†	27.2 ± 12.3†
	2.4%	15.9 ± 7.4†	15.0 ± 20.7†	5.0 ± 11.2†	0.3 ± 0.7†	3.0 ± 6.6†
Isoflurane	0.8%	67.0 ± 27.8	89.5 ± 19.2	55.4 ± 30.4†	24.1 ± 27.8†	54.9 ± 30.6*
	2.4%	24.6 ± 14.0†	33.8 ± 20.8*	22.1 ± 36.1†	0.0 ± 0.0†	16.6 ± 37.0†
	4.8%	4.6 ± 4.2†	0.0 ± 0.0†	2.9 ± 6.4†	0.0 ± 0.0†	0.0 ± 0.0†
Enflurane	0.6%	74.3 ± 17.3*	94.9 ± 7.6	77.6 ± 15.1	25.4 ± 18.6†	42.3 ± 14.8†
	1.8%	61.6 ± 14.3†	80.9 ± 17.4	37.4 ± 24.8†	10.1 ± 10.9†	12.4 ± 9.7†
	3.6%	20.8 ± 7.6†	54.6 ± 13.2†	4.4 ± 6.4†	0.0 ± 0.0†	0.0 ± 0.0†

*$P < 0.05$ versus control. †$P < 0.01$ versus control.

TABLE IV Effects of anaesthetics on the latency of cortical response induced by electrical optic chiasma stimulation ($n = 5$, % of control, mean ± SD)

Agent	Inspired conc.	Component 1	2	3	4	5
Halothane	0.4%	104.1 ± 2.0	107.1 ± 4.4	106.6 ± 7.2	105.9 ± 7.1	101.8 ± 3.2
	1.2%	109.4 ± 5.5	111.5 ± 5.1	111.1 ± 5.2	111.7 ± 7.5	107.9 ± 9.3
	2.4%	123.8 ± 15.8†	154.2 ± 28.8	N.D.	N.D.	N.D.
Isoflurane	0.8%	103.9 ± 3.4	104.3 ± 2.1	105.6 ± 5.4	111.6 ± 5.4	106.4 ± 18.8
	2.4%	118.0 ± 6.0*	119.8 ± 7.9	119.4 ± 5.1	N.D.	N.D.
	4.8%	134.4 ± 9.5†	N.D.	N.D.	N.D.	N.D.
Enflurane	0.6%	100.3 ± 1.8	102.0 ± 2.4	102.2 ± 1.0	104.1 ± 1.4	102.3 ± 5.1
	1.8%	101.1 ± 2.3	104.1 ± 2.5	103.9 ± 2.8	105.5 ± 1.0	108.3 ± 6.3
	3.6%	114.5 ± 4.0†	122.8 ± 10.7	N.D.	N.D.	N.D.

*$P < 0.05$ versus control. †$P < 0.01$ versus control. N.D.: not detected, statistical analyses not be carried out in these components.

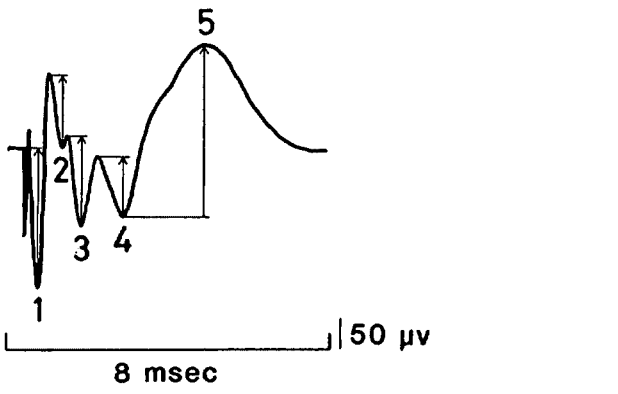

FIGURE 8 Cortical response to electrical stimulation of the optic radiation. The response is similar to that of the stimulation of the optic chiasma (Figure 7), but the latency of the responses are shorter by about 1 ms due to the absence of the thalamic relay.

negative component increased markedly at 3.6% enflurane.

Discussion

All anaesthetics studied suppressed both the background reticular cell and EEG activities in a dose-dependent manner. However, the degree of suppression by halothane was less than that induced by isoflurane and enflurane at similar MAC concentrations. The greater suppression induced by isoflurane and enflurane was, however, associated with some phasic activation in reticular cell firing, which appeared simultaneously with the EEG spikes. The phasic activation during enflurane anaesthesia was greater than that seen with isoflurane. In contrast to the background activity, the reactive capability assessed by visual evoked responses was suppressed by halothane and isoflurane but was facilitated with enflurane. The facili-

TABLE V Effects of anaesthetics on the amplitude of cortical evoked response induced by electrical optic radiation stimulation ($n = 5$,% of control, mean ± SD)

Agent	Inspired conc.	Component 1	2	3	4	5
Halothane	0.4%	96.4 ± 4.4	102.0 ± 11.2	96.1 ± 9.0	72.9 ± 17.1	86.4 ± 22.3
	1.2%	90.2 ± 6.1*	99.6 ± 12.4	84.9 ± 11.8	53.9 ± 16.6*	67.8 ± 19.2*
	2.4%	78.6 ± 6.1†	114.8 ± 22.4	94.3 ± 16.9	75.5 ± 20.4	61.2 ± 13.5†
Isoflurane	0.8%	93.9 ± 10.2	103.2 ± 9.7	88.1 ± 9.5	31.1 ± 28.6†	56.0 ± 9.9†
	2.4%	78.5 ± 9.8†	90.5 ± 34.7	35.4 ± 22.8†	33.7 ± 21.0†	13.0 ± 15.0†
	4.8%	59.9 ± 12.5†	74.0 ± 56.4	22.5 ± 24.0†	12.0 ± 16.5†	7.8 ± 10.7†
Enflurane	0.6%	85.4 ± 6.5†	89.1 ± 6.5	82.2 ± 5.4	39.4 ± 28.3†	62.1 ± 18.1*
	1.8%	75.3 ± 5.3†	83.0 ± 8.2*	39.4 ± 17.5†	12.4 ± 16.9†	21.6 ± 14.2†
	3.6%	65.5 ± 4.8†	85.9 ± 14.0	46.0 ± 24.3†	35.1 ± 48.3†	20.4 ± 28.0†

*$P < 0.05$ versus control. †$P < 0.01$ versus control.

TABLE VI Effects of anaesthetics on the latency of cortical evoked response induced by electrical optic radiation stimulation ($n = 5$, % of control, mean ± SD)

Agent	Inspired conc.	Component 1	2	3	4	5
Halothane	0.4%	105.0 ± 1.3	108.4 ± 7.3	106.1 ± 9.7	108.6 ± 10.0	104.5 ± 6.1
	1.2%	107.4 ± 2.4†	114.2 ± 9.4	108.3 ± 9.6	109.6 ± 10.3	106.4 ± 7.0
	2.4%	109.6 ± 5.9†	115.9 ± 12.6	113.6 ± 11.7*	123.0 ± 15.5†	118.7 ± 10.0†
Isoflurane	0.8%	104.3 ± 7.0	103.7 ± 2.2	103.1 ± 2.5	103.9 ± 6.0	104.9 ± 5.8
	2.4%	106.3 ± 8.4	115.7 ± 5.8	109.8 ± 5.1	122.2 ± 11.7	112.4 ± 4.8
	4.8%	110.1 ± 13.6	124.9 ± 7.2	117.1 ± 8.4*	N.D.	N.D.
Enflurane	0.6%	102.9 ± 4.3	101.8 ± 2.4	102.4 ± 3.4	100.4 ± 5.4	98.0 ± 6.0
	1.8%	104.5 ± 6.2	106.2 ± 2.2	104.2 ± 3.9	100.4 ± 5.5	89.1 ± 9.4
	3.6%	110.3 ± 10.4*	112.6 ± 8.0†	112.1 ± 7.0†	N.D.	N.D.

*$P < 0.05$ versus control. †$P < 0.01$ versus control.

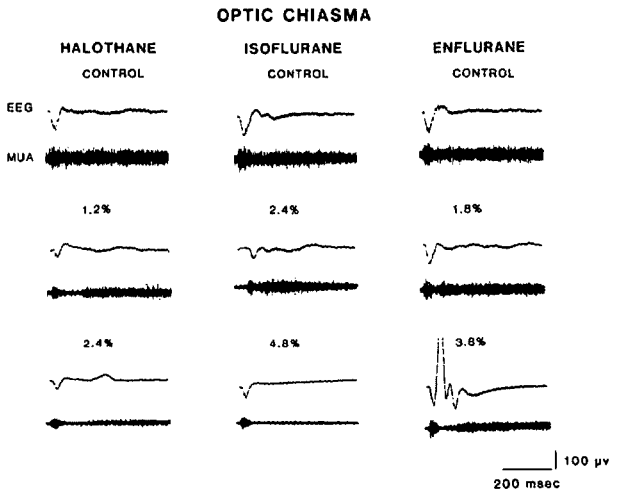

FIGURE 9 Effects of anaesthetics on the response of optic chiasma to the photic stimulation in EEG and MUA. The upper traces are EEGs, and the lower traces are MUA responses to the photic stimulation in the optic chiasma. The EEG responses are decreased in amplitude by anaesthetics except by 3.6% enflurane. The EEG response at 3.6% enflurane was considerably augmented. The envelopes of MUA responses are suppressed by all concentrations of anaesthetics.

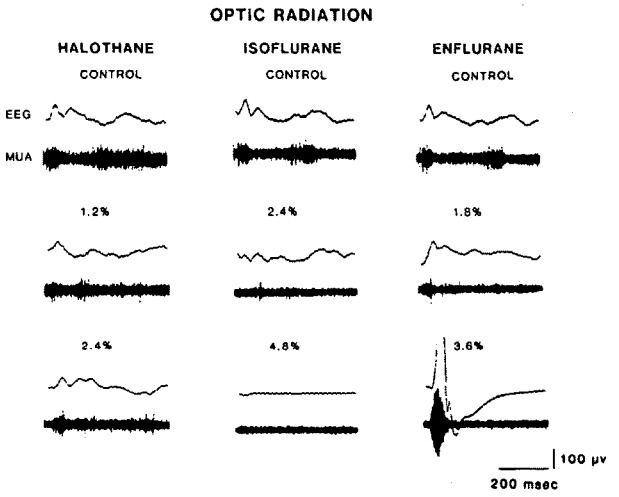

FIGURE 10 Effects of anaesthetics on the response of optic radiation to photic stimulation in EEG and MUA. The amplitude of the EEG responses was depressed by halothane and isoflurane, but was augmented by enflurane. The envelope of MUA response was suppressed by halothane and isoflurane, but was augmented by 3.6% enflurane.

tation of reactive capability by enflurane was dose-related and was greatest at deep levels of anaesthesia, when repetitive stimulation induced generalized tonic-clonic convulsions. These findings indicated that halothane suppressed the reactive capability most and the background activity least, enflurane augmented reactive capability but suppressed background activity most, and the actions of isoflurane were intermediate.

Suppression of reactive capability and hypnotic actions, which are the major components of general anaesthetic agents, are related to each other in an intricate manner. By definition, MAC is measured by the suppression of purposeful withdrawal response to noxious stimulation,[6] and may be reflected by changes in reactive capability and in the background activity of CNS neural components. Hypnotic action represents the action of anaesthetics on the level of vigilance, which is a tonic state of the CNS and may be reflected by the changes in background activity of CNS neurons. This indicates that, even if the suppression of the ongoing CNS neuronal activity is small, if the suppression of reactive capability is great, the potency is also great when assessed on a MAC basis. Sensory evoked responses reflect reactive capability.

Facilitation of reactive capability by enflurane and the lack of effect of isoflurane indicates the necessity of greater suppression of the ongoing cell activity as assessed by the multi-unit activity. Although the oil/gas partition coefficients are similar, the MAC values of enflurane and isoflurane are greater than that of halothane. Greater suppression of ongoing cell firing was produced by enflurane and isoflurane at the same MAC level. We reported previously that, of the conventional inhalation anaesthetics, enflurane was exceptional as it had little effect on the suppression of nociceptor-driven spinal cord response in spinal cats, while most anaesthetics suppressed it to considerable degrees.[7] Such a lack in spinal cord mechanism of analgesic action may also explain the greater MAC of enflurane. The weak ability of enflurane and isoflurane to suppress the reactive capability of the CNS might be related to some excitatory actions of these agents: spikes in EEG, and augmentation in amplitude of visual evoked response by enflurane and the shortening of the latent period by isoflurane, all indicate facilitation, and not suppression, of the reactive capabilities of these anaesthetics.

The high amplitude EEG spikes, which appear spontaneously and by stimulation during deep enflurane anaesthesia, and the generalized seizures induced by repetitive stimulation at deep enflurane anaesthesia are well known.[8–10] Isoflurane also induces similar EEG spikes, which are not associated with myoclonic jerkings and repetitive stimulation does not induce generalized seizure.[5,12,13] The present study demonstrated the difference in the neurophysiological properties of these spikes. Phasic enhancement in reticular cell firing, which was associated with the EEG spikes, was greater with enflurane than with isoflurane. Photic stimulation produced EEG spikes with enflurane but not with isoflurane. Mori and Winters[4] previously postulated that whether or not the EEG spikes during anaesthesia were associated with myoclonic jerking was determined by whether the EEG spikes were associated with enhancement in the reticular multi-unit activity. A similar postulate was suggested by Rodin *et al.*[14] who reported that the EEG spikes associated with enhancement of reticular multi-unit activity were associated with myoclonic jerking and those not associated with enhancement of the reticular multi-unit activity were not associated with myoclonic jerking in the case of pentylenetetrazol-induced EEG spikes. The present study confirmed the previous postulate. Enhancement of the surface negative component of the sensory evoked response is indicative of the convulsive property of pentylenetetrazol.[15] The present study confirmed that the surface negative component was enhanced by a convulsive dose of enflurane.

Deep enflurane anaesthesia enhanced the amplitude of visual evoked response and produced EEG spikes. Such augmentation was not produced by either isoflurane or halothane. The augmentation of response by enflurane was associated with prolongation of the latent period for the peak. With stimulation at the optic chiasma or at the visual cortical radiation to bypass the retina, the response was not augmented but was suppressed by deep enflurane anaesthesia. This suggests the role of the peripheral receptor to produce augmentation. Furthermore, the multi-unit response induced by visual stimulation was enhanced in the optic radiation, but suppressed in the optic chiasma. This indicated the role of thalamic relay for the augmentation of response.

In summary, both isoflurane and enflurane have some CNS stimulating actions, which are characterized by an epileptoid state, while halothane has little, if any, of such action. These epileptogenic properties may provide some difficulty when these agents are applied clinically: the need for supplementation with muscle relaxants is greater in the case of these epileptogenic agents. The compensation of the epileptogenic activity by nitrous oxide has been reported previously by this laboratory.[16] It is our conclusion that the suppression of reactive capability is a factor in determining the ease of clinical application of anaesthetics, and if this property is weak, supplementation with muscle relaxants and/or nitrous oxide is required.

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