

## The Effects of Several Anesthetic Agents on the Neuronal Reactive Properties of Thalamic Relay Nuclei in the Cat

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The effects of several anesthetics on the responsiveness of thalamic relay nuclei, the nucleus centrum medianum (CM) and the nucleus ventralis posterolateralis (VPL), were studied in galamine-immobilized cats with electrodes chronically implanted in their brains. Spontaneous activity and activity evoked by stimulation of the skin were monitored by recording multiple-unit activity (MUA). Halothane decreased MUA, cyclopropane enhanced it, and ketamine produced a change in the spontaneous firing pattern. Nitrous oxide and ether produced no consistent change. All agents produced depression of evoked activity. The depression was more profound in the CM than in the VPL. The anatomic basis for this difference is discussed. (Key words: Neuronal responsiveness; Thalamic relay nuclei; Multiple-unit activity; Nitrous oxide; Diethyl ether; Cyclopropane; Ketamine.)

THE CHIEF AIM of an anesthetic agent, protection of the patient from distressing and dangerous effects of necessary surgical procedures, entails sensory block for analgesia and mental quiet for unconsciousness.<sup>1</sup>

The reactive properties of the brain depend not only upon the effectiveness of transmission of neuronal signals but also upon the condition of spontaneous firing of the neurons existing prior to and during stimulation.<sup>2</sup> Thus, the degree of sensory block and the level of vigilance may not be entirely independent.

Utilizing the technique of monitoring the activity of a large population of neuronal units, we demonstrated in previous studies<sup>3-7</sup> that different anesthetics induced unconsciousness by variously modifying the neuronal firing pattern of the brain-stem reticular core, *i.e.*, pentobarbital and halothane depressed spontaneous firing, cyclopropane enhanced it, and ketamine changed the pattern.

In the present report, the relationship between the level of spontaneous firing and the reactivity of neurons to peripheral stimulation in the thalamic relay nuclei during various stages of anesthesia is described. Some of the results have been presented as a preliminary note.<sup>8</sup>

### Methods

#### PREPARATIONS

Three adult cats with electrodes chronically implanted in their brains and two acutely prepared cats were used. The structures from which electrical activity patterns were recorded were: anterior suprasylvian gyrus, nucleus ventralis posterolateralis (VPL) and nucleus centrum medianum (CM). Cortical electrodes consisted of stainless steel screws drilled to reach the dura. The subcortical electrodes consisted of stainless steel wires 0.2 mm in diameter insulated with epoxyite-resin except at the tip of the cut end. From these wire electrodes EEG and multiple-unit activity (MUA) were obtained simultaneously. The placement of the electrode for obtaining VPL activity was guided while recording MUA. The VPL electrode was anchored where the greatest MUA response was elicited by touching the pad on the side contralateral to the side on which recording was being done. When MUA was re-

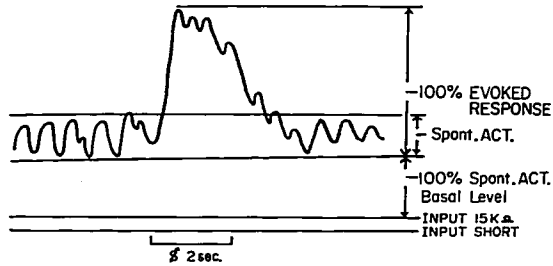
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FIG. 1. Schematic representation of measurement of the basal level and fluctuation of spontaneous MUA and the size of evoked MUA from the amplitude-demodulated tracing. The lowest horizontal line is obtained by inserting a short in the input to the cat, and the parallel line above it is obtained by inserting a 15-k $\Omega$  resistor at the input. The distance between these two lines is considered to be the system noise. The third line from the bottom represents the basal level of spontaneous MUA and the fourth, the peak of spontaneous activity during 2 seconds prior to stimulation.  $\sqsubset$  indicates the period of stimulation of the paw pad. The fifth (top) line represents maximum evoked activity. The mean of these values, obtained during the control period, was taken as 100 per cent activity.



corded monopolarly with the reference in the frontal sinus bone, a marked response was obtained by touching the skin gently even after ip administration of 40 mg/kg pentobarbital. The placement of the CM electrode was accomplished following the stereotaxic atlas of Jasper and Ajmon-Marsan.<sup>9</sup> Both electrode positions were verified histologically after the experiments.

#### RECORDING

Our techniques for recording MUA have been described.<sup>4-6</sup> MUA was obtained through a high-frequency band-pass filter, the peak frequency response of which was centered at 1,300 Hz, with 3-db decreases at 600 and 2,500 Hz. This signal was amplified and averaged with a rectifying circuit with the smoothing-time constant set at 50 msec. The integrated signal was recorded on the DC channel of a polygraph simultaneously with the EEG from the same electrode. The system noise level was estimated to be the DC level obtained by inserting a 15-k $\Omega$  resistor and a short across the input in place of the cat.

The basal level of spontaneous activity was measured as the distance from the base of the MUA tracing to the 15-k $\Omega$  resistor line, and the value obtained during the preanesthetic control period was set as 100 per cent basal level activity. The fluctuation of spontaneous firing was measured as the width of the excursion from the baseline to the peak when no

stimulation was given, and this value was expressed as per cent of the control basal level. The evoked activity was measured as the distance between the basal level during the 2 seconds prior to stimulation and the peak of elevation induced by stimulation (fig. 1). The mean of ten trials during the unanesthetized control state was arbitrarily set as 100 per cent reactivity, and activity levels during anesthesia were expressed as per cent of control.

#### STIMULATION

Stimulation was applied to the skin of the contralateral paw pad. Two subdermal needles, 10 mm apart, were inserted about 3 mm in depth. The train of square-wave pulses was applied for 2 seconds through an isolating unit: 0.5 msec duration and 100 pulses/sec. The intensity of the stimulation voltage was adjusted to about 30 per cent above the threshold voltage to induce the maximum response in the MUA of the CM. About 10 cm proximal to the stimulation site the total circumference of the extremity was covered with a saline-dipped cotton sponge, which was grounded. During the control period, succeeding stimulations were separated by intervals of at least 3 minutes, during which times the EEG patterns and the levels of MUA returned to prestimulation values. Since the changes induced by stimulation disappeared earlier during anesthesia, shorter intervals of 1 to 2 minutes were enough during anesthesia.

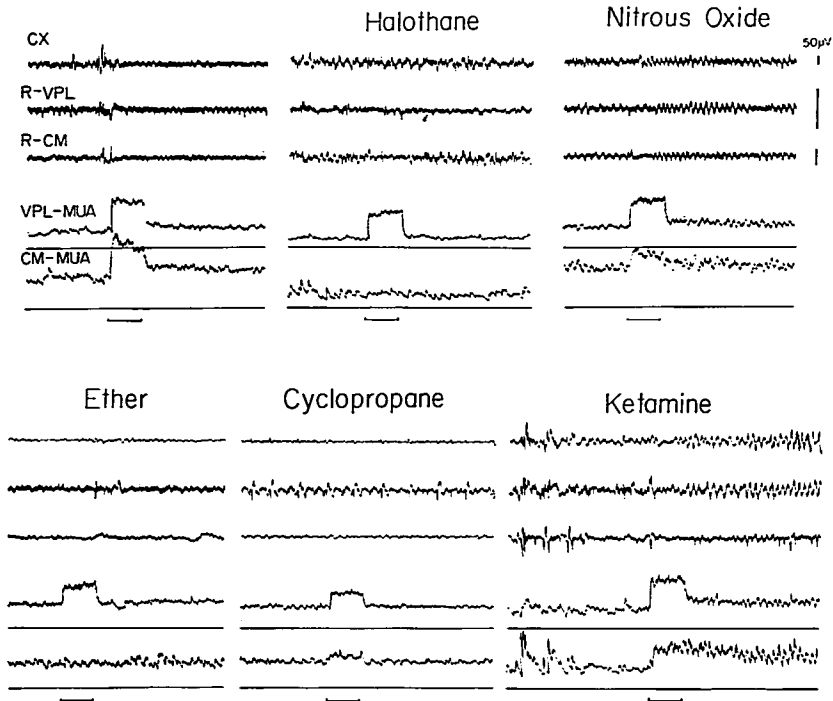


FIG. 2. Records obtained from a single cat in different experimental sessions. Upper left, control record before a halothane experiment. The studies of nitrous oxide and cyclopropane were done in one experimental session and those of ether and ketamine in another. This figure shows only the greatest degrees of depression of MUA in the nucleus ventralis posterolateralis (VPL) and the nucleus centrum medianum (CM) during the various periods of anesthesia. CX, R-VPL, R-CM; EEG records from the anterior suprasylvian gyrus, nucleus ventralis, posterolaterals, and nucleus centrum medianum, respectively. VPL-MUA, CM-MUA: amplitude-demodulated tracings of multiple-unit activity from the VPL and the CM. —: period of stimulation for 2 seconds. All records made during anesthesia correspond to the times indicated by arrows in figures 3 to 7.

#### ADMINISTRATION OF DRUGS AND EXPERIMENT

The drugs examined in chronic preparations were: halothane, 0.5, 1.0, and 2.0 per cent; nitrous oxide, 80 per cent; ether, 5 and 10 per cent; cyclopropane, 10, 30, and 50 per cent, ketamine, 2 + 2 mg/kg iv. Any one or two of these agents were examined in a single experi-

mental session lasting more than 2 hours. The intervals between experiments were longer than seven days. Because of the possibility of daily biological variation and inconsistency of the positions of stimulation electrodes, the control values of evoked responses varied to some extent from one experiment to the next. Thus, the results for the one cat from which the

most consistent control values were obtained throughout the study are presented.

Since the present study was attempted only to elucidate the relationship between spontaneous activity and the reactive property of neurons, we did not attempt to determine dose-effect relationships. Thus, the concentrations of anesthetics were increased gradually until moderate effects in the reactivity of neurons in response to stimulation were observed. In preparation for administration of an anesthetic agent, each cat was anesthetized by halothane initially, a tracheal tube was inserted, gallamine, 20 mg/hour, was administered iv, and respirations were set at 13 ml/kg tidal volume with a rate of 30/min. After endotracheal intubation, halothane inhalation was discontinued. Two hours later the experiment was started. Inhalation agents were administered by the nonbreathing method.

Two acutely-prepared cats were subjected to a study of the effects of halothane-induced hypotension on spontaneous and evoked MUA. These animals were given 2 per cent halothane only.

Experiments on the acute and chronic preparations differed in that in the acute preparations the electrodes were fresh, and about 5 ml of 2 per cent lidocaine were infiltrated into the wound margin and at the pressure point of the stereotaxic apparatus. After 60 min of administration of 2 per cent a steady state was reached and 0.001 per cent norepinephrine in physiologic saline solution was infused iv for 10 min to restore the control level of arterial pressure and permit examination of changes in spontaneous and evoked MUA before and during norepinephrine infusion.

During the courses of acute and chronic experiments rectal temperatures were maintained between 36 and 38 C by covering the cats' bodies with a mattress containing hot water.

## Results

### SPONTANEOUS ACTIVITY

Changes of MUA in the CM and the VPL were almost parallel following all agents studied, although the degrees of changes in the two nuclei differed. When MUA in the CM increased during administration of a given

agent, MUA in the VPL also increased, and *vice versa*. The changes were greater in the CM than in the VPL (fig. 2).

During administration of halothane the basal level of spontaneous MUA decreased to about 25 per cent of control, while fluctuation did not change markedly (fig. 3).

During administration of nitrous oxide (fig. 4), ether (fig. 5), and 10 per cent cyclopropane (fig. 6), the directions of changes of basal level and fluctuation in both nuclei were variable, not only from animal to animal but also during administration of constant concentrations; e.g., during administration of nitrous oxide the basal level increased to 150 per cent in both the VPL and the CM at 10 to 20 min and then returned to control, while fluctuation increased by about 50 per cent (fig. 4).

Administration of 30 per cent cyclopropane increased the basal level in the CM to 130-150 per cent of controls, but the basal level was decreased by 50 per cent cyclopropane (fig. 6).

Intravenous administration of ketamine (2 + 2 mg/kg) decreased the basal level while it increased fluctuation (fig. 7).

### EVOKED ACTIVITY

All agents studied induced depression of evoked activity in both the CM and the VPL, although the depression was much more profound in the CM (fig. 2).

The effect of halothane was most variable. During light anesthesia, transient increases (10-15 per cent) of evoked activity occurred occasionally in both the VPL and the CM, while moderate depression of the basal levels of spontaneous MUA was observed. The depression of evoked activity in the VPL was only 20-30 per cent at a time when moderate to complete depression in CM responsiveness occurred (fig. 3).

Administration of 80 per cent nitrous oxide induced 40-50 per cent depression in the CM when depression of evoked activity in the VPL was only about 10 per cent (fig. 4).

Administration of ether induced complete disappearance of evoked activity in the CM when that of the VPL was depressed to about 75 per cent. Further deepening of anesthesia induced further suppression of evoked activity in the VPL (fig. 5).

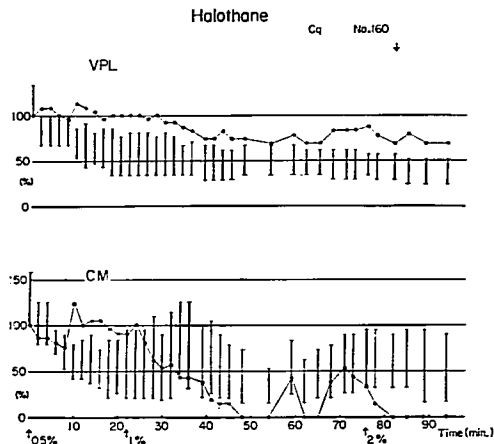


FIG. 3. Spontaneous and evoked activity in the nucleus ventralis posterolateralis (VPL) and the nucleus centrum medianum (CM) during halothane anesthesia. The bottom of each vertical bar represents the basal level and the length represents the fluctuation during the 2 sec prior to stimulation. Evoked activity in this and succeeding figures is shown by ●—●. At zero time the mean of ten control trials, taken as 100 per cent activity, is shown. The evoked activity in the CM was variable during inhalation of 0.5–1.0 per cent halothane. However, 2 per cent halothane blocked the response completely. The depression of response in the VPL was only 20–25 per cent.

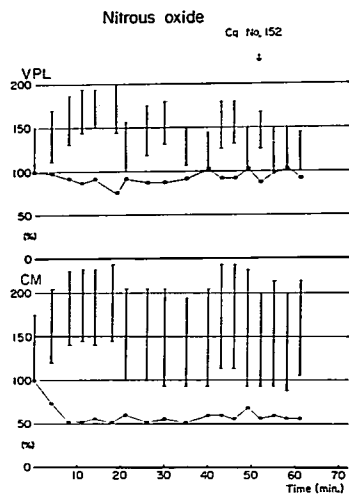


FIG. 4. Effects of nitrous oxide anesthesia. Symbols are the same as those in figure 3. During nitrous oxide anesthesia, the evoked activity in the VPL was depressed only slightly (0–15 per cent) while that in the CM was depressed to 50–60 per cent of the control value.

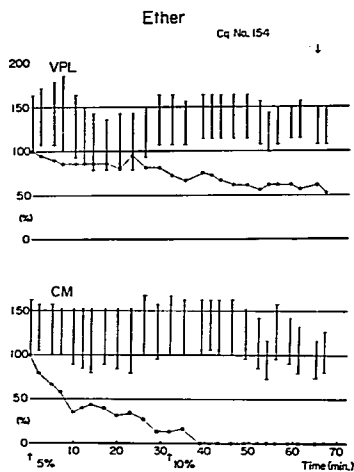


FIG. 5. Effects of ether anesthesia. Symbols are the same as those in figure 3. Depression of the evoked response in the CM occurred at a time when spontaneous activity did not change essentially. In the early phase of 100 per cent block of evoked activity in the CM, depression in the VPL was 25–30 per cent. Higher concentrations of ether depressed the VPL response progressively more.

During cyclopropane anesthesia the evoked activity levels in both the CM and the VPL were progressively depressed with increasing anesthetic depth. Complete block of evoked activity in the CM was noted when the VPL response was depressed to 65–75 per cent of control (fig. 6).

Following ketamine, the evoked activity in the CM was reduced to 30–40 per cent of control when depression of the VPL response was only 10–20 per cent (fig. 7).

#### INTERACTION OF CNS AND CARDIOVASCULAR EFFECTS OF HALOTHANE

The acute preparations had systolic arterial pressures of 160–170 mm Hg, which fell to 70–75 mm Hg in 60 min of administration of 2 per cent halothane. At this time the evoked responses in the CM and the VPL were 20–45

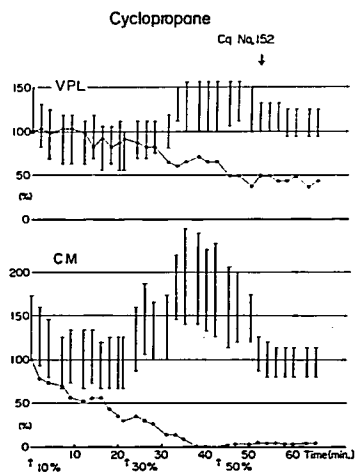


FIG. 6. Effects of cyclopropane anesthesia. Symbols are the same as those in figure 3. During light anesthesia (10 per cent), the basal level of spontaneous activity was depressed slightly; during moderate anesthesia (30 per cent), it was enhanced, and during deep anesthesia (50 per cent) it decreased again. The evoked activity was depressed progressively. In the initial phase of 90–100 per cent depression of evoked response in the CM, the depression of VPL response was 25–30 per cent.

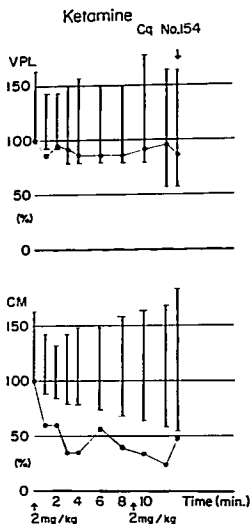


FIG. 7. Effects of ketamine anesthesia. Symbols are the same as those in figure 3. Following ketamine, the tonic pattern of MUA changed to grouping-firing, resulting in increased fluctuation, although the basal level was depressed progressively. The depression of evoked activity in the VPL was also less significant than that in the CM.

per cent and 67–78 per cent of control values, and they remained unchanged even after elevation of arterial pressure to preanesthetic control levels by iv infusion of norepinephrine.

#### Discussion

Unfortunately, in the present study moderate respiratory alkalosis must have been present, since our previous study<sup>5</sup> utilizing rabbits indicated that a tidal volume of 13–14 ml/kg with a ventilation rate of 20/min gave  $P_{aCO_2}$  values in the range of 27.5 to 37.3 mm Hg. One and a half times that rate with the same tidal volume was employed in the present study. Thus, the present results must have been contaminated by hypocarbic effects on the CNS. Although there is no evidence that hypocarbia affects the CNS effects of various anesthetic agents in the same directions, some

definite differences among different agents were demonstrated.

The present study revealed that there was no direct and simple relationship between the spontaneous activity and the reactivity of thalamic neurons, *i.e.*, the anesthetics induced either depression (halothane), inconsistent change (nitrous oxide, ether, and 10 per cent cyclopropane), enhancement (30 per cent cyclopropane), or dysrhythmia (ketamine) of spontaneous MUA, while reactive capabilities were reduced or abolished by all agents, especially in the CM.

In the present study, the CM must be considered from two points of view. It functions as the rostral end of the ascending reticular-activating system,<sup>10-12</sup> although there are some functional differences from the midbrain reticular formation.<sup>13, 14</sup> It also relays impulses from the spinothalamic tract<sup>15</sup> (or diffuse tegmental pathway)<sup>16</sup> and/or the cervicothalamic tract,<sup>16</sup> which are supposed to transmit pain sensation. Although the presynaptic component of the VPL is highly complex, being composed of at least six identifiable afferent components, the major difference between these two nuclei for the purposes of the present study is that, as the afferent input from peripheral sensory organs, the VPL has both lemniscal and spinothalamic input, while the CM has only spinothalamic input.<sup>19</sup> Further, structurally, the termination of the spinothalamic tract is fine, resembling reticular axons in the continued richness of their collateralization.<sup>19</sup> Randt *et al.*<sup>20</sup> reported that systems constituted of thin axons are more susceptible to anesthetics than those with thick axons. Monitoring single-unit activity in the VPL, Mallart *et al.*<sup>21</sup> found that only 11 units of 55 somatosensory neurons responded to stimulation of the spinothalamic tract. This implies that about 20 per cent of the evoked activity in the VPL is composed of the spinothalamic influx, and the remaining 80 per cent belongs to the lemniscal influx. Supposing that 50 per cent of the spinothalamic influx is blocked by anesthetics with the lemniscal input left intact, the evoked activity in the CM may be reduced to 50 per cent of control, while that of the VPL might be reduced by only half of 20 per cent, or 10 per cent of control. A re-

duction of this amount might be buried in the variance of the experimental data. This might be the basis for reports that anesthetics had little, if any, effect on EEG evoked responses in the VPL.<sup>22, 23</sup> The present study confirmed the findings of Mallart *et al.*, *i.e.*, when 50 per cent reduction in the evoked activity in the CM was induced, only about 10 per cent reduction occurred in the VPL, and in the early phase of 100 per cent reduction of the response in the CM, the response in the VPL was reduced by 20-30 per cent. Further deepening of anesthesia reduced the VPL response more, indicating that higher concentrations of anesthetics depressed even the thick-axon component of the lemniscus.

The results of the present study indicate that anesthetic agents affect neuronal spontaneous activity and reactive capability differently, and further, that different anesthetics have different effects on the spinothalamic and lemniscal components.

The authors thank Professor S. Sakakibara for making available laboratory facilities.

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### The Anesthesiologist's Bookshelf

**Advances in Cardiology. Volume 6. Mechanical Devices for Cardiopulmonary Assistance.** Edited by R. H. BARTLETT, P. A. DRUNKER, AND P. M. CALLETT. Basel, S. Karger, 1971. Pp. 195. \$16.30.

Sponsored by the Association for the Advancement of Medical Instrumentation, a group of scientists representing many disciplines met in Boston in March 1970 to discuss the problems and progress in prolonged support of life by mechanical circulation and respiration. The contributions of the participants are collected in this volume under the headings of "Secondary Flows to Augment Gas Transfer in Membrane Lungs," "New

Techniques of Interest in Blood Oxygenation," "Prolonged Extracorporeal Support with Membrane Lungs," and "Prolonged Circulatory Assistance."

Because of damage to blood, disc and bubble oxygenators are dismissed, and interest is centered around silicone membranes. Methods for improved diffusion of oxygen into the artificial blood stream by induced secondary currents are presented. Some of the technical problems in fabrication of silicone membranes are discussed. The feasibility and advantages of utilizing mixtures of blood and biologically inert liquids having high

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