The Effects of Anesthetics on Reticular and Cortical Activity

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The effects of thialbarbital, diethyl ether, and propanidid on the midbrain reticular formation and the cerebral cortex were studied in the cat. Thialbarbital caused marked depression of the activity of the reticular formation and only slight depression of cortical activity. Inhalation of ether caused early depression of synaptic input to the reticular formation without significantly influencing the functional state of the reticular formation itself. In the cortex ether caused early and marked depression. Propanidid caused less inhibition of the reticular formation than did thialbarbital. The significance of the enhancement of cortical responses in the mechanism of the production of general anesthesia by propanidid is not yet clear. The data suggest that there is no universal mechanism of general anesthesia which can explain the effects of different general anesthetics on various structures of the central nervous system. (Key words: Diethyl ether; Barbiturates; Propanidid; Reticular formation; Cerebral cortex.)

The classification of general anesthetics according to their effects on cortical and brainstem structures¹ was forgotten after the role of the brain-stem reticular formation (RF) in maintaining the state of wakefulness was demonstrated. Since the reports by Moruzzi and Magoun² and French et al.,³ it has been firmly established that general anesthesia is the result of the abolition of the corticofugal influence of the RF, a structure believed to be most sensitive to the action of general anesthetics. Other recent investigations, however, have questioned this theory. It has been shown that during the first stage of ether anesthetic the EEG desynchronization is the result of RF excitation.⁴ Schlag and Brand⁵ found persistent spontaneous activity of single reticular neurons when the evoked potentials were absent during sensory stimulation. Moreover, considerable differences among the clinical and EEG pictures during general anesthesia caused by different anesthetics make it doubtful that these various changes are of the same origin or that they are always related to RF blockade. To test possible differences in the effects of various general anesthetics on different parts of the brain, the actions of diethyl ether, thalbarbital, and propanidid on the midbrain RF and the cerebral cortex have been studied and are the subject of this paper.

We estimated the functional state of the cortex by determining callosal potentials (CP's), that is, potentials evoked in the cortex in response to electrical stimulation of a symmetrical point on the contralateral hemisphere. Chang⁶ showed that CP's represent a response to electrical stimulation moving through the corpus callosum without involving the subcortical structures. Therefore, CP's were chosen as a test to estimate the functional state of cortical neurons and the degree of their inhibition caused by a given general anesthetic. The condition of the RF was estimated by two indices. Any sensory stimulation may produce an evoked potential in the RF.⁷ Because of this, the system is called nonspecific. These evoked potentials have been shown to be very sensitive to general anesthetics.⁸ It is also known that synaptic transmission of input signals to the RF is accomplished by a mediator different from that in the RF itself.⁹ Therefore, besides recording evoked potentials in the RF (which reflect the activity of the input into this structure), we also recorded the reaction of EEG desynchronization resulting from elec-
trical stimulation of the RF. This test made it possible to estimate the excitability of the RF per se.9

Methods

Thirty-five adult cats were used in these experiments. The trachea and the femoral vein of each cat were cannulated with the cat under ether anesthesia. After injection of tubocurarine chloride, ventilation was assisted mechanically. The animal’s head was fixed in a stereotaxic instrument. Pressure points and wound margins were infiltrated with 0.5 per cent lidocaine (Xylocaine). The cerebral cortex was widely exposed and the dura folded back. Exposed pial surface was covered with warm mineral oil. A double electrode, 0.5 mm in diameter, was inserted into the RF (coordinates A +2; L 3.5; H −1.5).10

The electrode in the RF could be connected by a switch to either the output of a stimulator (for RF stimulation) or the input of

Fig. 1. Effect of intravenous thiobarbital on the EEG during electrical stimulation of the reticular formation (Cat 45). Arrows = onset and end of stimulation. Calibration 200 μV; time mark, 1 sec. 1) EEG of conscious cat, stimulation, 2 v; 2) EEG of conscious cat, stimulation, 3 v; 3) after injection of thiobarbital (10 mg/kg), stimulation, 2 v; 4) stimulation, 3 v; 5) stimulation, 4 v; 6) after injection of thiobarbital (15 mg/kg), stimulation, 2 v; 7) stimulation, 3 v; 8) stimulation, 4 v.
Fig. 2. Effect of ether on the EEG during electrical stimulation of the reticular formation (continuation of fig. 1). 1) EEG four hours afterwards, stimulation, 2 v; 2) stimulation, 3 v; 3) inhalation of 8 per cent ether, stimulation, 2 v; 4) stimulation, 3 v; 5) stimulation, 4 v; 6) EEG 30 minutes after the end of inhalation, stimulation 2 v. Other indices are the same as in fig. 1. Amplification is slightly increased.

an electroencephalograph (for recording RF evoked potentials resulting from electrical stimulation of a paw). To elicit CP’s, a bipolar stimulating electrode with an interpolar distance of 1 mm was placed on the surface of the suprasylvian gyrus. The recording electrode was placed on a symmetrical point on the contralateral hemisphere. The spontaneous EEG and the EEG during RF stimulation were recorded by the same electrode. An indifferent electrode was placed in the temporal muscle. The eight-channel electroencephalograph (Galileo R-32) was used for EEG recording. Evoked and callosal potentials were photographed from the screen of a two-beam oscilloscope, Cl-18. A two-channel universal electronic stimulator, ESU-I, with radiofrequency outputs was used for stimulation.

The duration of rectangular impulses for the paw stimulation (through needle electrodes) and for RF stimulation was 0.5 msec; each impulse for cortical stimulation lasted 0.2 msec.

Ether was given through a vaporizer, "Krasnogvardeez," connected to the inlet of pump respirator. Concentrations delivered were gradually increased from 2 per cent to 15–20 per cent, approaching the beginning of stage IV of general anesthesia. Stages were determined according to the EEG, on the basis of the method of Faulconer,11 who has demonstrated a close correlation of concentrations of ether in arterial blood with changes in the EEG. Thialbarbital, 1 per cent, and propanidid, 2.5 per cent, were injected intravenously. After the initial injection of thialbarbital (3–5 mg/kg) similar doses were injected at 5–8-minute intervals. After each injection all measurements were made while general anesthesia progressed from stage I to stage III.
The same procedure was used with propanidid, but for obtaining deeper stages of general anesthesia the doses were gradually increased. With both agents measurements were made immediately after injection. EEG was recorded continuously. Usually, a single cat was used to test two or three anesthetics. Intervals of two to three hours after propanidid or ether and not less than four to five hours after thiobarbital elapsed before administration of the next anesthetic. The lengths of the intervals were determined as follows: after complete recovery of all reactions tested, an hour (for propanidid) or two hours (for ether and
Fig. 4. Effect of intravenous propanidid on the EEG during electrical stimulation of the reticular formation (Cat I1). 1) EEG of conscious cat, stimulation, 2 v; 2) EEG of conscious cat, stimulation, 3 v; 3) after injection of propanidid (10 mg/kg), stimulation, 2 v; 4) stimulation, 3 v; 5) stimulation, 4 v; 6) EEG 30 minutes after injection of propanidid, stimulation, 2 v. Other indices are the same as in fig. 1.

thalbarbital) elapsed before administration of the next agent. The orders of administration of the agents were varied. Rectal temperature was maintained at 37-38°C during the experiment by means of a heater and an infrared radiator.

Results

The EEG of the conscious curarized normally-ventilated cat showed a persistent beta-rhythm with single delta and theta waves. EEG desynchronization was caused by high-frequency (150-250 Hz) RF stimulation. EEG desynchronization became more pronounced as the voltages of impulses increased (figs. 1-4, curves 1-2). The threshold of desynchronization was usually about 2 v. Thalbarbital in doses of 10-15 mg/kg caused appearance on the EEG of high-amplitude alpha-like waves with a frequency of 8-12 Hz (the so-called "barbiturate spindles"), corresponding to stage I2 of general anesthesia according to the classification of Guedel12 and Artuso,13 or stage II according to the classification of Schneider et al.14 (fig. 1).

Electrical stimulation of the RF did not induce EEG desynchronization at this stage of general anesthesia, but sometimes a slight acceleration of cortical waves was seen during stimulation (fig. 1, curves 3-5). Doses of 20-25 mg/kg of thalbarbital caused appearance on the EEG of high-amplitude (more than 500 μV) delta and theta waves, corresponding to stages III1-III212,13 or stage III14 of general anesthesia. Electrical stimulation of the RF at this stage had no effect on the EEG even after significant increases in stimulation voltage (fig. 1, curves 6-8).

The potentials in the RF evoked by stimulation of the paws of conscious cats were positive-negative or negative only, and their amplitudes rose slightly as stimulation voltages
increased. The negative waves lasted 15–30 msec and the latencies lasted 12–20 msec. The thresholds of the evoked potentials were usually 3–15 v. In stage I of barbiturate anesthesis (as estimated from the EEG) the amplitudes of evoked potentials decreased, but they persisted at all stimulation voltages. In stage III, RF evoked potentials decreased sig-
Fig. 6. Effect of ether on callosal (upper rows) and RF (lower rows) evoked potentials. Indices are the same as in fig. 5.

significantly, but small-amplitude potentials persisted. The durations of the evoked potentials increased significantly (fig. 5, II).

CP’s of the conscious cats consisted of positive-negative oscillations with latencies of 2-4 msec. At 2-3 threshold stimulation the positive wave was about 200-300 µV and the negative wave, about 600-800 µV. In stage I of barbiturate anesthesia there was no significant change in CP amplitude or duration. The spread of individual CP’s increased, which may have been related to a summation of the CP’s and high-amplitude potentials appearing in the EEG in this period. In stages III, of barbiturate anesthesia CP amplitude did not increase significantly. However, the range of individual CP’s did increase (fig. 5, I).

Inhalation of ether, which causes well-known EEG changes, did not influence the EEG desynchronization threshold during RF electrical stimulation until stage III of anesthesia (classifications of Guedel, Artusio, and Schneider and Thomalske). Even during the appearance of the theta waves with a frequency of 1-2 Hz corresponding to stage III of general anesthesia, electrical stimulation of the RF caused marked EEG desynchronization (fig. 2). Evoked potentials in the RF disappeared at the very beginning of inhalation of ether, in stage II of anesthesia. Sometimes it was possible to elicit evoked potentials in the RF at 2-4 threshold stimulation, but the amplitude decreased significantly. In stages I-II of ether anesthesia the evoked potentials in the RF were completely blocked (fig. 6, lower rows), whereas the marked spontaneous activity of this structure persisted. The amplitudes of CP’s decreased considerably in stage I of ether anesthesia, especially during weak stimulation. In stages I-II, CP responses to stimulation at threshold or twice threshold value disappeared in most experiments. A strong stimulation (four times threshold or more) caused a slight response (fig. 6, upper rows).

Propanidid in doses of 7-10 mg/kg caused appearance of high-amplitude EEG waves (up to 1 mv) of 8-10-Hz frequency (fig. 3). In this stage of general anesthesia electrical stimulation of the RF did not influence EEG amplitude, but with stronger stimulation the frequency of cortical potentials was also higher (fig. 3, curves 3-5). Propanidid in doses of 10-15 mg/kg caused appearance in the EEG
of high-amplitude theta and delta waves. RF electrical stimulation did not usually cause EEG desynchronization (fig. 3, curves 6-7). Sometimes, at the termination of propanidid action, during the period of theta waves, RF stimulation enhanced the frequency of the cortical electrical potentials (fig. 4, curves 4-5). Propanidid in doses of 7-10 mg/kg slightly decreased the amplitude of evoked potentials in the RF; the spread of amplitudes in single potentials increased (fig. 5, IV). At the deepening of general anesthesia (appearance of theta and delta waves on the EEG), the amplitudes of evoked potentials in the RF decreased considerably, especially with weak stimulation; the negative waves decreased more than the positive waves. Owing to the appearance of high-amplitude spontaneous activity in the RF, the spread of individual potentials increased in comparison with stage I (fig. 5, IV). CP's increased slightly during the appearance in the EEG of waves with a frequency of 7-10 Hz, although at threshold stimulation this augmentation did not occur (fig. 5, III); the duration of the potentials did not change. The actions of two or all three of the anesthetics investigated were studied in every experiment, using different sequences and different combinations. No effect of the first-used agent on the effects of the second or third was ever found. All data are summarized in table 1.

**Discussion**

The data obtained show the existence of considerable differences in the actions of the
general anesthetics investigated. The effect of thialbarbital corresponded to the classical picture describing general anesthesia as a result of RF blockade. Depression of the EEG desynchronization reaction and of the evoked potentials in the RF in stages I,II reflected the progressive inhibition of this structure by thialbarbital. The cortical excitability, which changed but little in these stages, showed that the direct effect of the thialbarbital on the cortex probably did not play an essential role in the development of general anesthesia, since the ability of cortical neurons to respond to direct stimulation showed no marked changes. Quite different effects were produced by ether anesthesia. The disappearance of the evoked potentials in the RF in stages I,II,III, ether anesthesia, described many times and confirmed by us, has always been interpreted as a proof of RF depression. However, the absence of threshold changes in EEG desynchronization during RF electrical stimulation does not confirm this interpretation. The disparity of these two indices of the condition of the RF during ether anesthesia may be explained by the fact that ether acts on the input to sensory pathways in the RF but not in the functional condition and the excitability of RF neurons themselves. Bradley, and Gilinsky and Ilyuchenko described the same correlation during the action of chlorpromazine, which blocks the synaptic structures of the input to the RF without influencing the activity of the activating system itself. The essential distinctions between these two phenomena are: the input blockade in the RF, as has been
(Amplitude of Callosal Potentials), Inputs of Reticular Formation
Reticular Formation (Threshold of Appearance of EEG
Values in Conscious Animals*)

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<th>Thalubarital</th>
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<td></td>
<td>Stage II Thresholds</td>
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<td>118.0 ± 12.9</td>
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<td>121.0 ± 22.9</td>
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<td>185.0 ± 42.1</td>
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Shown with chlorpromazine, does not influence the state of wakefulness, does not induce loss of consciousness and, therefore, cannot be regarded as causing general anesthesia. These data may be interpreted to mean that the anesthetic action of ether is not the result of blockade of ascending arousal influences of the RF either. On the contrary, ether has an early depressant action on the cortex. Reduction of CP amplitudes, observed from the very beginning of the inhalation of ether in stages I-III of anesthesia, reflects the progressive depression of the activity of the cortical neurons and their ability to react to stimulation.

The suggestion that the cortex is depressed during ether anesthesia has been confirmed by investigations of cortical unit activity. Schlag and Brand,5 using microelectrodes, showed total depression of cortical neuronal spontaneous activity at the very beginning of ether anesthesia. Golovchinsky15 described depression of the cortical neuronal spontaneous activity which paralleled the level of anesthesia during thalubarital anesthesia, whereas inhalation of ether entirely blocked the impulse activity of the same neurons in stage I2. On the basis of this information, we suggest that the primary site of action of ether is the cerebral cortex, and that it is blockade of this structure, but not of the RF, that causes general anesthesia.

In contrast to ether and thalubarital, propanid caused pronounced facilitation of cortical reactions by increasing CP amplitudes. The nature of this facilitation is not yet clear. On the contrary, the EEG desynchronization during the RF electrical stimulation disapp
One of the suppositions upon which the "reticular theory" of general anesthesia is based is the hypothesis of greater sensitivity to the action of general anesthetics of polysynaptic structures with large numbers of synaptic relays, compared with oligosynaptic structures. Since the RF is a classical example of a structure with a large number of synaptic relays, its great sensitivity to the action of general anesthetics, postulated by French et al., was thus explained. The data presented in this paper argue against this hypothesis. The preservation of the activity of polysynaptic structures during ether anesthesia coexistent with blockade of oligosynaptic pathways leading to the RF and monosynaptic pathways transmitting CP's testifies to the fact that responsiveness does not depend on the length of neuronal chains or the complexity of the synaptic organization; instead, the depression depends on the specific interaction of the given general anesthetic and the chemical structure of the given synapses. Valdman was the first to make this suggestion, and there are confirmatory experimental data. Thus, in some microelectrode studies it has been shown that barbiturates exert a depressant effect on the cholinergic synapses while ether does not.

These data indicate that the main role of the general anesthetics in the development of inhibition is based not on the complexity of the structure but on specific interactions of molecules of the general anesthetics with chemically heterogeneous synapses in the central nervous system.

These data permit a more adequate evaluation of the EEG. In some experiments with propanidid the electrical stimulation of the RF during the onset of stage III of anesthesia did not induce EEG desynchronization. During recovery from anesthesia at the same stage (by EEG estimation), electrical stimulation of the RF caused EEG desynchronization (fig. 4). Thus, identical EEG patterns with the same general anesthetic may correspond to different states of the RF or central nervous system depression, depending upon whether the EEG is recorded during onset of general anesthesia or during recovery. Care must be exercised in evaluating the data obtained with the EEG even with a single general anesthetic.

On the basis of earlier data and those obtained in this study, it is possible to draw important conclusions concerning the genesis of the EEG. The depression of discharges of the cerebral neurons during persistence of the EEG suggests that the mechanism of the generation of the cell discharge differs essentially from the mechanism of the generation of postsynaptic potentials; the latter can persist even during complete depression of impulse activity. As is commonly believed, the recorded EEG oscillations are the sum of the postsynaptic potentials; persistence of the EEG during the depression of cerebral unit discharges justifies this approach, arguing against the EEG as a summation of cerebral cell discharges. Since postsynaptic potentials reflect the afferent activity reaching the cortex, the recorded EEG activity reflects mainly the activity of subcortical structures but not that of the cortex itself. This is most obvious during inhalation of ether, when all the cycles of the EEG, corresponding to the anesthetic stages, occur against a background of deep depression of impulse activity of cortical neurons.

We conclude that there is no uniform mechanism of the development of general anesthesia which can explain the effects of different general anesthetics on the central nervous system. The fading of the RF evoked potentials during ether anesthesia does not prove the depression of this structure, but reflects the depression of synaptic input to the RF without any significant influence on the functional state of reticular neurons. The decrease in amplitude of the CP's suggests that ether causes primary blockade of the cerebral cortex but not of the RF. Barbiturate anesthesia markedly depresses the RF but depresses the cortex only slightly. The RF depression may be regarded as the cause of barbiturate-induced general anesthesia. Propanidid anesthesia is not accompanied by cortical depression, and causes less pronounced depression of the RF than that produced by thialbarbital. Therefore, these peculiarities of propanidid are not likely to be regarded as the cause of general anesthesia.

References

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Drugs

PROPRANOLOL  Propranolol in very small doses (average: 1 mg/81 kg body weight) was used successfully to treat intra- and postoperative tachyarrhythmias in 20 patients. This dose does not reduce the pulse rates of normal subjects even following administration of atropine. Increased sympathetic tone which was partially blocked by the drug was probably present in these patients. No adverse effects on blood pressure or other vital functions were observed. (List, W. F., and Marsoner, H. J.: On the Dosage of the Beta-receptor Blocker Propranolol in the Intra- and Postoperative Treatment of Tachyarrhythmias, Der Anaesthetist 18: 394 (Dec.) 1969.)