The Effects of Halothane and Methoxyflurane on Recovery Cycles of Click-evoked Potentials from the Auditory Cortex of the Cat

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Halothane and methoxyflurane in therapeutic concentrations produced dose-related depression of the auditory recovery cycle in the cat. The anesthetics tested had these subtle but definite effects on central nervous system function at a time when amplitude of cortical evoked responses was not depressed.

MEASUREMENT of the auditory recovery cycle[1-6] consists of the application of identical paired auditory stimuli, the first as the conditioning and the second as the test stimulus, and calculation of the ratio between the amplitude of the second and first evoked cortical responses as a function of the interval between the two. The auditory recovery cycle has proven to be a reliable, reproducible, objective index of central nervous system reactivity which is more sensitive than measurement of amplitude of evoked response alone.[4-6] Although reports of the effects of many central nervous system depressants on evoked responses are numerous, only a few reports [7-9] of the effects of recently-introduced halogenated inhalation anesthetics on evoked responses are available. Their effects on the recovery cycle have not been reported. The present investigation was undertaken to obtain further information about the central nervous system actions of halothane and methoxyflurane. Effects on the recovery cycle of the auditory cortex of the cat have been studied using computer techniques, which allow the means of a large number of evoked responses to be obtained even in the presence of variability of response and the small signal-to-noise ratios observed at various depths of general anesthesia.

Methods

Bipolar electrodes were chronically implanted over the A-one (A1) auditory cortex in two adult female cats (3.0 kg. and 2.9 kg.) anesthetized with intraperitoneal pentobarbital (Nembutal). Accurate placement of the electrodes was assured by constant monitoring of the click-evoked response (CER). The electrodes, 200 μ in diameter, were of stainless steel, insulated with teflon except at the distal 1.0 mm. The more superficial of the two electrodes had a circular loop at its tip and was placed over the dura, the deeper electrode being 2 mm. from the loop and piercing the dura. The bipolar electrodes and an indifferent electrode were then connected to a Winchester socket permanently fixed with dental cement to the skull. Two weeks later control observations were made while the unanesthetized animals rested quietly. Since the state of alertness of the unanesthetized animal affects the auditory cortical recovery cycle,[5,6] animals were studied only when awake (as determined by EEG) but resting quietly. Pairs of identical clicks were applied through earphones every two seconds. The interval between them was increased from 1 msec. to 20 msec. in increments of 1 msec.; from 20 msec. to 100 msec. in increments of 10 msec.; and from 100 msec. to 200 msec. in increments of 20 msec. Following control observations, general anesthesia was induced and the observations were repeated. Varying depths of

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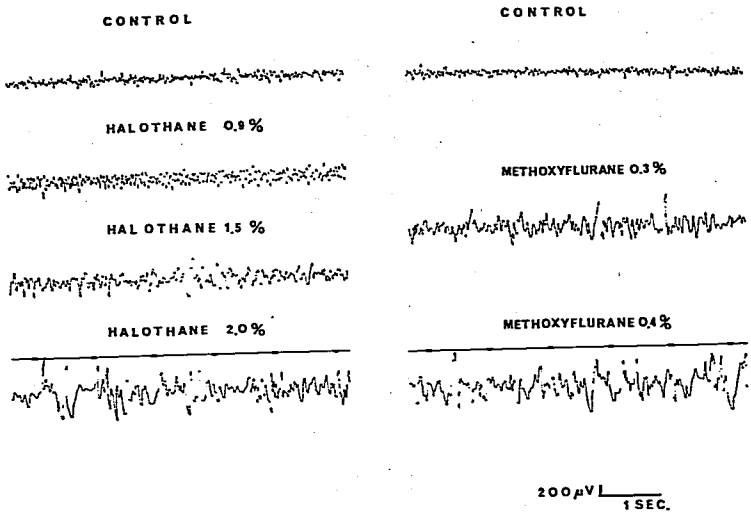

FIG. 1. EEG tracing during control study and anesthesia.

halothane anesthesia were studied twice each and different depths of methoxyflurane anesthesia were studied only once in each of the two cats. Intervals of 7–14 days intervened between experiments.

Stimuli used were approximately twice threshold intensity. Because the intensity of click stimuli modifies auditory cortical recovery cycles,[4–6] rigidly uniform stimuli with square waves of 400 mv. intensity and 0.03-msec. duration were produced, using a type 162 Tektronix waveform generator and a type 161 pulse generator applied to the cats by Audiovox 9C receivers (earphones). Earphones rather than overhead speakers were employed to reduce variability in the sound field.[11] The CER was amplified through a type 122 Tektronix preamplifier with 3 db points at 8 cycles for low-frequency response and at 10 kilocycles for high-frequency response. These were displayed on a type 502 Tektronix cathode-ray oscilloscope, fed into a model FT1052 Fabritek signal-averager computer, summed in groups of 32 pairs having identical intervals, and written out on the X-Y plotter. The ratio of amplitude of the second response to that of the first (R_2/R_1) was measured at each interstimulus interval. The EEG was recorded from the same bipolar electrodes using a model 7 Grass polygraph with half-amplitude cut-off at 1.5 cycles for low-frequency response and at 60 kilocycles for high-frequency response.

Anesthesia was induced using a semiclosed, face mask system into which oxygen flowed at 4 liters per minute after passage through a Fluotec® vaporizer (halothane), or a Pentec® vaporizer (methoxyflurane). Following induction, endotracheal intubation was performed without muscle relaxants to preclude possible effects on responses.[12] Anesthesia was maintained with controlled respiration in a nonrebreathing system using a Harvard small-animal ventilator, the intake of which was connected to a reservoir bag filled with the oxygen–anesthetic mixture. Respirations were maintained at 30 per minute with tidal volumes of 50–70 ml. to avoid hypercarbia. At least 30 minutes of exposure to each concentration of each anesthetic was employed

to allow stabilization of the anesthetic level as determined by EEG. The concentrations of halothane studied were 0.9 per cent, 1.5 per cent and 2.0 per cent. The concentrations of methoxyflurane studied were 0.3 per cent and 0.4 per cent.

The EEG was used to monitor the depth of anesthesia. As shown in figure 1, in an unanesthetized cat resting quietly the tracing showed relatively low-voltage (30–100 μv.), β rhythm (20–25 cps.) activity; during 0.9 per cent halothane anesthesia, amplitude increased (100–200 μv.), and frequency became slower (15–20 cps.), with regular rhythm and spindling; during anesthesia with 1.5 per cent halothane there was a further increase in amplitude (100–300 μv.), and a further decrease in frequency (α rhythm of 8–15 cps.); with 2 per cent halothane the amplitude became extremely large (200–600 μv.), interspersed with spike forms and periods of suppression, and the frequency became θ rhythm. The EEG pattern during anesthesia with 0.3 per cent methoxyflurane was similar to that of 1.5 per cent halothane, although the frequency was slightly higher; during 0.4 per cent methoxyflurane the EEG pattern corresponded to that of 2.0 per cent halothane as seen in figure 1. Concentrations below 0.3 per cent halothane or 0.1 per cent methoxyflurane were associated with the animals' coughing on the endotracheal tubes. Concentrations above 2.5 per cent halothane or 0.6 per cent methoxyflurane were associated with such marked depression of evoked responses that accurate measurement of amplitude became impossible. The EEG, pupillary size, respiratory rate and tidal volume, pulse and arterial systolic blood pressure (minimum pressure necessary for cessation of pulsation recorded by plethysmographic method) were recorded at the end of the period of stabilization and during recording of recovery cycles. Rectal temperature was kept constant at 37–39° C. by means of a cooling mattress, to preclude changes in the auditory cortical recovery cycle due to changes in temperature.[4]

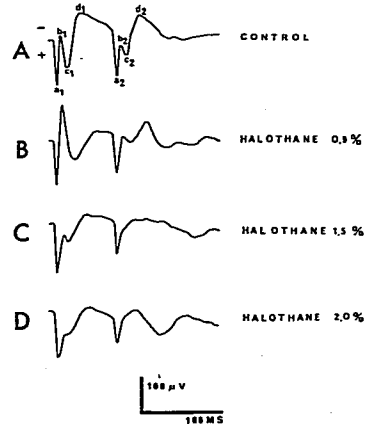

FIG. 2 A–D. Typical computer-averaged evoked responses from the A-one (A1) auditory cortex of Cat 1 following paired click stimuli with 70-msec. interval, formed by computer summation of 32 responses. Note the progressive depression of amplitude of a_2 relative to that of a_1 as the concentration of halothane is progressively increased.

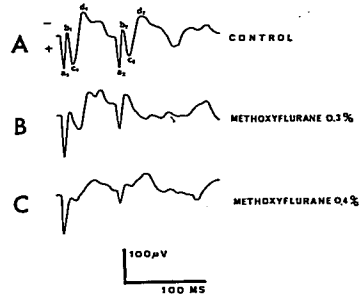

FIG. 3 A-C. Typical computer-averaged evoked responses from the A-one (A1) auditory cortex of Cat 1 following paired click stimuli with 70-msec. interval, formed by computer summation of 32 responses. Note the progressive depression of amplitude of a_2 relative to that of a_1 as the concentration of methoxyflurane is progressively increased.

Results

The form, amplitude and latency of the computer-averaged cortical evoked responses (CER) following 32 pairs of identical click stimuli (CS) with 70-msec. intervals, before

TABLE 1. Amplitude, Latency of Onset and Latency of Peak of the First Positive Wave of Cortical Evoked Response to the First of Paired Click Stimuli*

	Cat 1			Cat 2		
	Amplitude (μv.)	Latency of Onset (msec.)	Latency of Peak (msec.)	Amplitude (μv.)	Latency of Onset (msec.)	Latency of Peak (msec.)
Control	123	5.5	9.8	183	5.9	11.0
Halothane 0.9%	148	5.4	10.3	210	5.8	11.1
Halothane 1.5%	135	5.8	11.1	200	6.0	11.5
Halothane 2.0%	130	6.0	12.9	56	6.4	13.7
Methoxyflurane 0.3%	146	5.7	11.2	190	6.8	12.5
Methoxyflurane 0.4%	125	6.0	12.0	71	7.0	13.0

* Each number represents computer-averaged value of 32 or 74 pairs of responses obtained in animals unanesthetized and anesthetized with halothane and methoxyflurane.

anesthesia, are shown in figures 2A and 3A. The first evoked response of the pair is made up of two surface positive waves (a_1 and c_1) divided by a surface negative wave (b_1) and followed by a second surface negative wave (d_1). During general anesthesia the shape of the response changed; with 0.9 per cent halothane (fig. 2B) a_1 and b_1 showed an increase in amplitude; with 1.5 per cent halothane (fig. 2C) b_1 and c_1 showed a reduction in amplitude; with 2.0 per cent halothane (fig. 2D) c_1 disappeared and the response became wider. The effect of methoxyflurane is shown in figures 3B and 3C. With 0.3 per cent

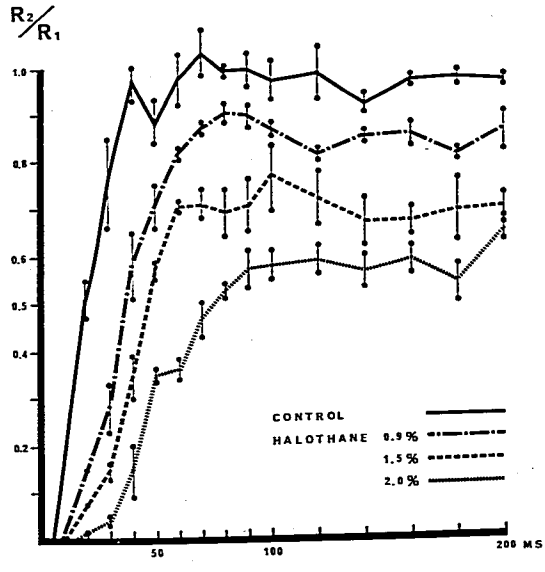

FIG. 4. Graphic representation of the recovery cycles of the evoked-response amplitude from the primary auditory cortex of Cat 1 unanesthetized and during exposure to 0.9 per cent, 1.5 per cent and 2.0 per cent halothane anesthesia. The intervals in msec. between the paired clicks are shown on the abscissa, and the ratio of the amplitude of the second response relative to that of the first response (R_2/R_1) is shown on the ordinate. Two sets of experiments are represented in this graph. For control and for each concentration of halothane, two dots are shown at a given inter-click interval, one dot representing computer-averaged ratios of 32 pairs of responses in one experiment and the other dot representing computer-averaged ratios of 32 pairs of responses in the second experiment. Lines drawn between the two dots show the average values of the two sets of experiments.

methoxyflurane (fig. 3B) c_1 decreased in amplitude; with 0.4 per cent methoxyflurane (fig. 3C) c_1 almost disappeared and was wider. The evoked responses of Cat 2 showed c_1 which was less prominent than that in Cat 1, probably due to variation in electrode location; the wave form also showed less change during general anesthesia. Significant increase in amplitude of b_1 seen in the first response of the pair during 0.9 per cent halothane anesthesia was not seen in the second response of the pair (fig. 2B). The form of the first positive wave in both the first response (a_1) and the second response (a_2) of the pair was least affected by the anesthetics; therefore, amplitude of a_1 and a_2 was measured for the recovery cycle (R_2/R_1). As shown in table 1, during anesthesia there was an increase in amplitude of a_1 with both anesthetics and at all concentrations, except in Cat 2 when 2.0 per cent halothane or 0.4 per cent methoxyflurane was administered, at which time there was also significant arterial hypotension; latency of onset and latency of peak were prolonged with higher concentrations of both halothane and methoxyflurane.

Control data from unanesthetized animals resting quietly (figs. 4–7) showed complete disappearance of the second response when the inter-click interval (ICI) was shortened below 6–7 msec. for Cat 1 and 5–6 msec. for Cat 2 (see table 2). Since an R_2/R_1 ratio of 0.6 was the maximum degree of recovery obtained during the deepest levels of anesthesia in this study, the ICI (in msec.) associated with a recovery cycle (R_2/R_1) of 0.6 was employed as a basis for comparison. Control data showed that a recovery cycle ratio of 0.6 occurred with ICI of 20–30 msec.; the ratio gradually increased as the ICI increased until, at intervals of 40 msec. and above, the ratio remained 0.9–1.0 in both animals.

The recovery ratio of the second evoked cortical response to the first as a function of ICI during halothane anesthesia is shown in figure 4 (Cat 1) and figure 5 (Cat 2). Data

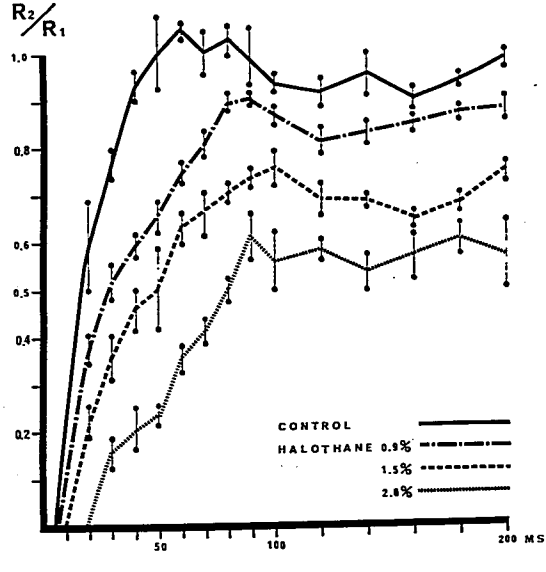

FIG. 5. Graphic representation of the recovery cycles of the evoked-response amplitude from the primary auditory cortex of Cat 2 unanesthetized and during exposure to 0.9 per cent, 1.5 per cent and 2.0 per cent halothane anesthesia. The intervals in msec. between the paired clicks are shown on the abscissa, and the ratio of the amplitude of the second response relative to that of the first response (R_2/R_1) is shown on the ordinate. Two sets of experiments are represented in this graph. For control and for each concentration of halothane, two dots are shown at a given inter-click interval, one dot representing computer-averaged ratios of 32 pairs of responses in one experiment and the other dot representing computer-averaged ratios of 32 pairs of responses in the second experiment. Lines drawn between the two dots show the average values of the two sets of experiments.

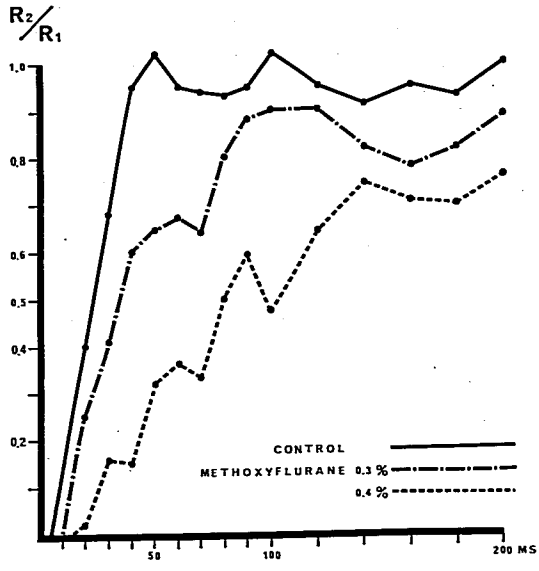

FIG. 6. Graphic representation of the recovery cycles of the evoked-response amplitude from the primary auditory cortex of Cat 1 unanesthetized and during exposure to 0.3 per cent and 0.4 per cent methoxyflurane anesthesia. The intervals in msec. between the paired clicks are shown on the abscissa, and the ratio of the amplitude of the second response relative to that of the first response (R_2/R_1) is shown on the ordinate. Each dot represents computer-averaged ratios of 32 pairs of responses.

obtained during 0.9 per cent halothane anesthesia showed complete disappearance of the second response when the ICI was shortened below 7 msec. in Cat 1 and 7–9 msec. in Cat 2. The recovery cycle (R_2/R_1) was 0.6 at ICI of 40–50 msec. and gradually increased as ICI increased until, at intervals of 60 msec. and above, the ratio remained 0.8–0.9 in both animals. During 1.5 per cent halothane anesthesia there was complete disappearance of the second response when the ICI was shortened below 9 msec. in Cat 1 and 9–10 msec. in Cat 2. The recovery cycle was 0.6 at intervals of 50–60 msec., gradually increasing as the ICI increased until, at intervals of 60–80 msec. and above, the ratio remained 0.6–0.8 in both animals. During 2.0 per cent halothane anesthesia there was complete disappearance of the second response when the ICI was shortened below 12–13 msec. in Cat 1 and 18 msec. in Cat 2. The recovery cycle was 0.6 at intervals of 90–100 msec. With intervals greater than 100 msec. the ratio remained 0.5–0.7 in both animals.

Data obtained during methoxyflurane anesthesia are shown in figure 6 (Cat 1) and figure 7 (Cat 2). During 0.3 per cent methoxyflurane anesthesia there was complete disappearance of the second response when the ICI was shortened below 9 msec. in Cat 1 and 8 msec. in Cat 2. The recovery cycle was 0.6 at intervals of 40–50 msec. and gradually increased as the ICI increased until, at intervals of 70–80 msec. and above, the ratio remained 0.8–0.9 in both animals. During 0.4 per cent methoxyflurane anesthesia there was complete disappearance of the second response when the ICI was shortened below 12 msec. in Cat 1 and 15 msec. in Cat 2. The recovery cycle was 0.6 at intervals of 80–90 msec.; with intervals greater than 90 msec. the ratio remained 0.6–0.8 in both animals.

The ICI associated with complete disappearance of the second CER progressively increased as concentrations of halothane and

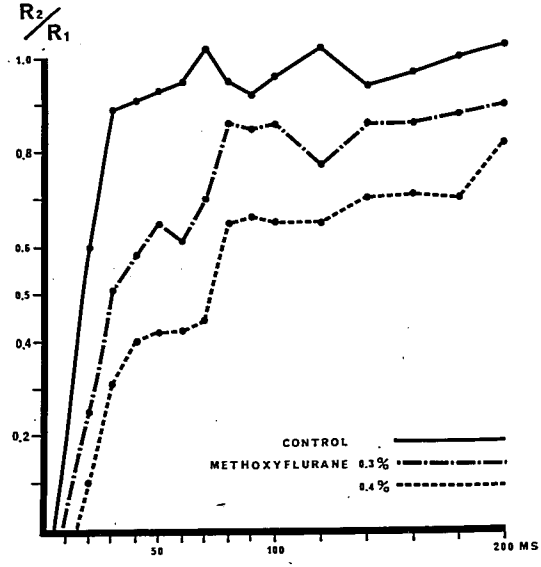

FIG. 7. Graphic representation of the recovery cycles of the evoked-response amplitude from the primary auditory cortex of Cat 2 unanesthetized and during exposure to 0.3 per cent and 0.4 per cent methoxyflurane anesthesia. The intervals in msec. between the paired clicks are shown on the abscissa, and the ratio of the amplitude of the second response relative to that of the first response (R_2/R_1) is shown on the ordinate. Each dot represents computer-averaged ratios of 32 pairs of responses.

methoxyflurane were increased. Deeper levels of anesthesia necessitated progressively longer ICI for the recovery cycle (R_2/R_1) to reach 0.6, the maximum degree of recovery obtained during the deepest levels of anesthesia, and caused shift of recovery curves progressively downward and toward the right. This indicated a dose-related depressant effect of halothane and methoxyflurane on the early phase of the recovery curve. When halothane and methoxyflurane were compared, 0.3 per cent methoxyflurane and 0.9 per cent halothane showed similar effects upon the recovery curve, with the curve obtained during 0.4 per cent methoxyflurane anesthesia fitting between the curves obtained for 1.5 per cent and 2.0 per cent halothane.

Vital signs of both animals were stable throughout, except in Cat 2 when, during the highest concentrations of both anesthetics, significant decreases in arterial blood pressure and evoked-response amplitude occurred. Carbon dioxide tension of the end expiratory air during controlled ventilation was 20–25 mm. Hg.

Discussion

This study was designed to evaluate the effects of inhalation anesthetics upon cerebral cortical function by measuring changes in-

TABLE 2. Inter-click Threshold, Inter-click Interval, and Maximum R_2/R_1*

	I.C.T. (msec.)		I.C.I. (msec.) for R_2/R_1 of 0.6	R_2/R_1 (maximum)
	Cat 1	Cat 2	Cat 1 and Cat 2	Cat 1 and Cat 2
Control	6–7	5–6	20–30	0.9–1.0
Halothane 0.9%	7	7–9	40–50	0.8–0.9
Halothane 1.5%	9	9–10	50–60	0.6–0.8
Halothane 2.0%	12–13	18	90–100	0.5–0.7
Methoxyflurane 0.3%	9	8	40–50	0.8–0.9
Methoxyflurane 0.4%	12	15	80–90	0.6–0.8

* I.C.T. (inter-click threshold) determined as the shortest inter-click interval expressed in msec. in order to evoke the second response of the pair corresponds to absolutely refractory period when the maximum stimulus is used. I.C.I. (inter-click interval) for a set ratio (0.6) of R_2/R_1 (the second response relative to the first response) is shown in msec. The maximum R_2/R_1 ratio obtained is shown in the last column.

duced in the auditory cortical recovery cycle, measurements which in themselves entail quantitation of the effect of anesthetics upon cortical evoked responses. As French *et al.*,[13] have demonstrated, at a time when general anesthetics have produced reversible depression of the reticular formation of the brain stem, transmission of afferent impulses from periphery to cerebral cortex via the classical lateral sensory pathways is relatively unaffected. In fact, as a result of reticular formation depression, the background cortical EEG may be depressed to the point[14] that afferent impulses transmitted to the cortex via the classical system are brought into a prominence greater than usual. Thus, Pradhan and Galambos[15] observed that whereas in deeper levels of anesthesia there was progressive depression in amplitude of the initial positive wave complex of the auditory cortical response evoked by a single click stimulus, under light or moderate depths of anesthesia the positive wave complex was increased in amplitude. Pradhan and Galambos[15] also showed a difference in response to anesthetics such as pentobarbital, paraldehyde, diethyl ether, and ethyl chloride on the one hand, and to chloralose and chloroform on the other, the latter giving more prompt, larger and longer enhancement of the positive wave complex.

In the present study the effects of halothane and methoxyflurane upon amplitude of auditory evoked responses as measured by amplitude of response to the first of paired clicks were increased except in the presence of concentrations of anesthetics great enough to produce an arterial hypotension severe enough to depress cortical potentials.[16] The present results are in agreement with the findings of Domino *et al.*,[8] that halothane and methoxyflurane likewise do not depress the visually-evoked response amplitude in man significantly and, in fact, enhance certain portions of the response when cardiovascular depression is avoided. The depression of cortical and subcortical click-evoked responses in cats reported by Winters *et al.*,[9] was noted in studies in which the concentrations of halothane employed (2–6 per cent) were high enough to be associated with progressive degrees of arterial hypotension. Sasa *et al.* (1967),[10] also reported that 1, 2, and 3 per cent halothane depressed responses from the auditory cortex and the inferior colliculus of cats anesthetized with diethyl ether for transection of spinal cord at the C_1 level. The depressant effects of arterial hypotension on the evoked responses, however, could not be excluded since vital signs were not recorded during the procedure.

Depression of the recovery cycle (R_2/R_1) may be due to an increase in amplitude of the first response (R_1) without change in the second response (R_2); to a decrease in amplitude of R_2 without significant change in R_1; or to an increase in R_1 associated with a simultaneous but lesser increase in R_2. Effects of anesthesia upon the amplitude of R_1 and R_2 with a 200-msec. interval between them are shown in table 3 in terms of percentage increase or decrease compared with control values obtained in the unanesthetized animal. With 0.9 per cent halothane and 0.3 per cent methoxyflurane, amplitudes of R_1 as well as R_2 were increased, suggesting that the mechanism responsible for the increase in R_1 amplitude also was affecting R_2 amplitude in the same direction, but to a lesser degree, and that an increase in R_1 amplitude was not the cause of the reduction in the recovery cycle. Further increases in the concentrations of anesthetics were associated with reduction in R_2 amplitude without depression of R_1 amplitude. With significant arterial hypotension in Cat 2, when 2.0 per cent halothane and 0.4 per cent methoxyflurane were administered, both R_1 and R_2 were decreased in amplitude, with a greater depression of R_2 than of R_1. Changes in the recovery cycle during anesthesia, *i.e.*, changes in R_2/R_1, were due to anesthetically-induced changes in amplitude of response to the second click (R_2), associated with an increase in amplitude of R_2 which was less than the concurrent increase in R_1 amplitude, or with depression of R_2 amplitude as the concentrations of anesthetics were increased further.

The phrase "absolute refractory period" is avoided in the above discussion because it varies according to the intensity of the stimulus. Absolute refractory periods of auditory

TABLE 3. Effects of Halothane and Methoxyflurane upon the Amplitude of R_1 and R_2 Responses with 200 msec. Intervals Between Them*

	Cat 1			Cat 2		
	R_1(%)	R_2(%)	R_2/R_1	R_1(%)	R_2(%)	R_2/R_1
Control	0	0	0.97	0	0	0.98
Halothane 0.9%	+20	+ 6	0.86	+14	+ 3	0.89
Halothane 1.5%	+ 9	−22	0.70	+ 9	−21	0.72
Halothane 2.0%	+ 5	−30	0.65	−70	−83	0.57
Methoxyflurane 0.3%	+18	+ 8	0.89	+ 3	− 7	0.90
Methoxyflurane 0.4%	+ 1	−22	0.76	−62	−69	0.82

* Shown in terms of percentage increase (+) or decrease (−) compared with control values obtained in the unanesthetized state. The third column for each animal shows the recovery cycle (R_2/R_1), each number representing a computer-averaged ratio calculated from 32 or 74 pairs of responses obtained in animals unanesthetized and anesthetized with halothane and methoxyflurane.

cortical evoked response during anesthesia have been reported in animals as 8 msec.,[2] 15 msec.,[5] 80 msec.,[17] or 100 msec.,[1] the variation probably being due to differences in stimulus intensity. When the stimulus is kept constant in intensity and duration, as in this study, the shortest inter-click interval necessary to evoke the second response of the pair (inter-click threshold) may be used to compare the rapidity with which the cortical excitability recovers. The graded increase noted in this study as the concentrations of anesthetics were increased seems to indicate progressive decrease of the cortical excitability.

The progressive shift of the recovery curves downward and toward the right during exposure to increasing concentrations of anesthetics (figs. 4–7) indicates that the recovery ratio (R_2/R_1) is decreased progressively at a given inter-click interval, and that progressively longer inter-click intervals are needed for a set recovery ratio (R_2/R_1) as the concentrations of anesthetics are increased. The shift of the recovery curves described, therefore, signifies a progressive depression of the cortical recovery function as the anesthetic concentrations are increased progressively.

The effects of low carbon dioxide tension upon the recovery function in the present study cannot be evaluated fully. However, the different effects of halothane and methoxyflurane at different concentrations at a time when ventilation was kept constant demonstrate a dose-related depressant effect of the anesthetics in the presence of hypocapnea.

The significance of the present study lies in the demonstration that halothane and methoxyflurane administered in anesthetic concentrations are associated with subtle alterations in cerebral cortical activity, alterations more subtle than can be detected by studies of cortical evoked response alone. The implication is that, although the anesthetics studied may, and in all probability do, have as their primary site of action the reticular formation,[7, 9, 13] they are not devoid of simultaneous effects on other portions of the central nervous system. Since the present study of the recovery cycle was undertaken exclusively as a study of the primary auditory cortex, further studies on subcortical structures are needed to clarify where and how anesthetics affect the recovery cycle of click-evoked potentials.

Summary

The effects of halothane and methoxyflurane on the recovery cycles of the primary auditory cortex were studied in cats bearing permanently-implanted electrodes. Using computer techniques, data were obtained in unanesthetized animals and the effects of anesthetics were studied in animals anesthetized solely by the test drugs.

The first positive wave of the click-evoked response was used to measure amplitude of the recovery cycle (R_2/R_1). Its amplitude increased with both anesthetics and at all concentrations except in Cat 2 when 2.0 per cent halothane or 0.4 per cent methoxyflurane was administered, at which time there was also sig-

nificant arterial hypotension. Latency of onset and latency of peak were both prolonged with higher concentrations of halothane and methoxyflurane.

The inter-click interval associated with complete disappearance of the second click-evoked response progressively increased as concentrations of halothane and methoxyflurane were increased. Deeper levels of anesthesia necessitated progressively longer inter-click intervals for the recovery cycle (R_2/R_1) to reach 0.6. This was the maximum degree of recovery obtained during the deepest levels of anesthesia, and caused shift of recovery curves progressively downward and toward the right, indicating a dose-related depressant effect of halothane and methoxyflurane on the early phase of the recovery curve. Effects of halothane and methoxyflurane at various concentrations upon the recovery curve were compared.

The present study indicates that halothane and methoxyflurane, administered in anesthetic concentrations, are associated with alterations in cerebral cortical activity more subtle than those which can be detected by studies of single cortical evoked response amplitude alone. These changes may be secondary to or in addition to those associated with reticular-formation depression. Further studies of subcortical structures are needed to clarify where and how anesthetics affect the recovery cycle of the auditory cortical evoked responses.

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