EFFECT OF CYCLOPROPANE ON THE MESENCEPHALIC RETICULAR FORMATION AND CEREBRAL CORTEX

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The effect of cyclopropane on evoked potentials in the mesencephalic reticular formation, on the desynchronization reaction of the EEG during electrical stimulation of the reticular formation, and on the transcallosal responses was studied in acute experiments on cats. Cyclopropane led to an early and marked depression of evoked potentials in the reticular formation. The threshold of the desynchronization response increased slightly with deepening of the cyclopropane anesthesia, but a desynchronization response continued until stage III_3. The amplitude of the positive wave of the transcallosal response was not significantly changed, while the amplitude of the negative wave decreased progressively as the anesthesia deepened.

The rapid depressant action of cyclopropane on evoked responses in the mesencephalic reticular formation (RF) has been described [11, 14, 17]. At the same time, very slight changes in spontaneous activity of RF neurons have been found even under deep cyclopropane anesthesia [8]. It has also been shown that cyclopropane causes depression of primary cortical responses [14].

It was decided to explain the causes of the conflicting results obtained by the investigation of global responses and behavior of single RF neurons, and also to compare the sensitivity of the cerebral cortex and RF to the action of this anesthetic.

The state of cortical function was assessed by the transcallosal response (TCR) and the state of RF function by two tests: the evoked potential (EP) in RF in response to sensory (electrical) stimulation of the skin, and the appearance of a desynchronization response of the EEG to direct electrical stimulation of RF.

EXPERIMENTAL METHOD AND RESULTS

The EEG and TCR in the suprasylvian gyrus were recorded in 20 cats immobilized with tubocurarine and maintained on artificial respiration. Stimulation of RF and recording of EP in this structure were carried out with the same double electrode. Cyclopropane mixed with oxygen was injected into the inlet of the artificial respiration apparatus. The method was described previously [2, 3].

The character of the EEG, TCR, and EP in the RF and also the effect of electrical stimulation of RF on the EEG have frequently been discussed in the literature [2, 7, 12, 16].

Inhalation of cyclopropane in a concentration which increased slowly from 10 to 40% caused a very slight increase in amplitude and a slight decrease in the frequency of the EEG, corresponding to stage I_2 of anesthesia [5, 10]. The threshold of the desynchronization response remained the same. In stage I_3–II the amplitude of the waves was appreciably increased; characteristic bursts of spindle-like activity with

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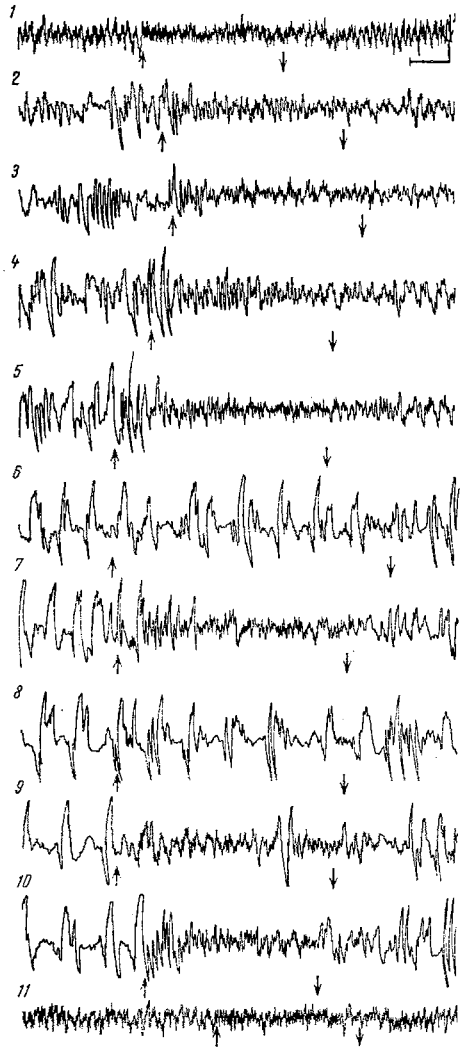

Fig. 1. Effect of inhalation of cyclopropane on the EEG during electrical stimulation of the reticular formation: 1) background; amplitude of stimulation 3V; 2) stage I_3-II of anesthesia, amplitude of stimulation 3V; 3) stage I_3-II of anesthesia, amplitude of stimulation 4V; 4) stage III_1, amplitude 4V; 5) stage III_1, amplitude 5V; 6) stage III_2, amplitude 5V; 7) stage III_2, amplitude 6V; 8) stage III_3, amplitude 6V; 9) stage III_3, amplitude 7V; 10) stage III_3, amplitude 8V; 11) 40 min after end of inhalation of cyclopropane, amplitude of stimulation 3V. Arrows indicate beginning and end of electrical stimulation; calibration of amplification 100 μV; time marker 1 sec.

a frequency of 8-10/sec, resembling "barbiturate spindles" in character, developed periodically. The threshold of the EEG desynchronization response was increased by 1-1.5 V (Fig. 1: 2 and 3). Deepening of the anesthesia to stage III_1, as shown by the appearance of a θ-rhythm and of single δ-waves on the EEG, led to a further increase in the threshold of the desynchronization response (Fig. 1: 4). An increase in the strength of the stimulus caused desynchronization of the EEG, but not immediately: the appearance of a β-rhythm was preceded by an initial decrease in amplitude of the dominant θ-rhythm which was then replaced by an α-like rhythm of low amplitude, after which (provided that the stimulation continued at unchanged strength) the typical desynchronization appeared (Fig. 1:5). The same pattern, although less marked, was also observed in the more superficial stages of anesthesia. After the end of stimulation, its effect did not disappear immediately, but waves characteristic of waking or a more superficial level of anesthesia persisted for some time on the EEG. In stage III_2 the EEG was dominated by a high-amplitude δ-rhythm with a frequency of 1-3/sec. The threshold of desynchronization continued to rise (Fig. 1:6). The character of the gradual "tailing off" into desynchronization became even more prolonged (Fig. 1:7). In stage III_3 the character of the electrical waves remained the same, but their frequency was reduced; in most experiments desynchronization of the EEG did not occur during electrical stimulation of RF, but in some cases a further increase in the voltage of stimulation once again produced the series of changes in the EEG waves toward the pattern of superficial anesthesia, as described above, sometimes as far as a β-rhythm (Fig. 1:9-10). As a rule summation of the alerting effects of reticular stimulation was observed; in stages III_2-III_3 frequently desynchronization did not arise in response to the first series of stimuli, but as they followed one another in rapid succession, a marked shift on the EEG was observed toward the pattern of more superficial anesthesia, after which desynchronization appeared in response to the third or fourth series of stimuli (Fig. 1:6 and 7).

In stage I_2, the EP in RF in response to threshold stimulation were completely suppressed; in most experiments the responses disappeared even when the voltage of the stimulating pulses was twice or three times the threshold level. In all experiments deepening of anesthesia to stage III_1 led to complete disappearance of EP in the RF in response to stimulation of the strength used (Fig. 2).

In stages I_2 and I_3–II of cyclopropane anesthesia, no consistent changes could be found in the amplitude of the TCR; an increase, a decrease, or no change in the amplitudes of both TCR waves were observed in different experiments. At these stages of anesthesia, the changes in TCR amplitude were not statistically significant. Deepening of the anesthesia led to more definite changes in the amplitude of the TCR. At stages III_2–III_3 there was a statistically significant decrease in the amplitude of the negative wave of the TCR; the amplitude of the positive wave increased slightly, but this increase again was not statistically significant (Fig. 3). The results of statistical analysis of the data are given in Table 1.

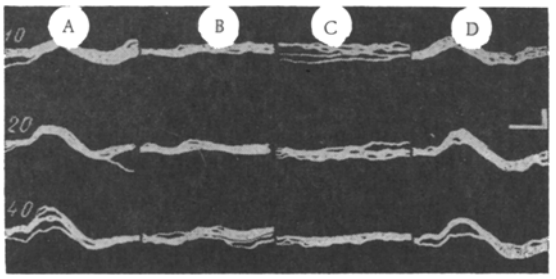

Fig. 2

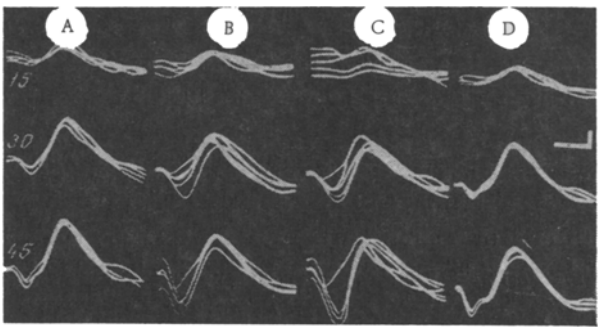

Fig. 3

Fig. 2. Effect of inhalation of cyclopropane on evoked potentials in mesencephalic reticular formation: A) background; B) stage I_3 of anesthesia; C) stage III_1 of anesthesia; D) 40 min after end of inhalation of cyclopropane; numbers on left show amplitude of stimulating pulse (in V); calibration of amplification 100 μV; time marker 20 msec. Positivity downward.

Fig. 3. Effect of inhalation of cyclopropane on transcallosal responses. Legend as in Fig. 2.

TABLE 1. Effect of Cyclopropane Anesthesia on Amplitude of Waves of Transcallosal Response*

Strength of stim. (thresholds)	Stage of anesthesia				
	I_2	I_3—II	III_1	III_2	III_3
	Positive wave				
I	87,4±29,0	136,5±49,2	116,2±25,3	114,5±21,5	124,4±39,4
II	95,3±23,8	136,5±49,2	116,2±25,3	114,5±21,5	124,4±39,4
III	97,3±27,6	144,0±61,5	132,0±34,6	125,8±35,3	124,0±51,5
	Negative wave				
I	79,4±20,0	101,8±39,0	94,3±33,4	64,9±22,6	55,8±22,6
II	78,3±17,5	111,2±36,5	72,9±12,3	68,5±13,8	61,0±11,7
III	103,2±31,4	92,9±17,4	80,5±16,6	77,3±13,5	74,0±22,9

*M ± m (in percent of results for waking animals).

The increase in the threshold of the EEG desynchronization response during electrical stimulation of RF as the general anesthesia deepened reflects the gradual depression of this structure by cyclopropane. Nevertheless, the possibility of evoking desynchronization of the EEG until the end of stage III is evidence that the ability of the neurons to generate spikes was undisturbed. The absence of depression of RF is also shown by the fact that, as described previously [8], spontaneous unit activity persisted even during deep cyclopropane anesthesia. The complete blocking of evoked potentials in RF side by side with preservation of spontaneous activity during the action of cyclopropane can be attributed to differences in the chemical structure and, consequently, in the sensitivity of synaptic endings of the collaterals of the afferent pathways and synapses in the RF itself to the action of this general anesthetic. The existence of such differences has also been demonstrated during the action of chlorpromazine [6]. Chlorpromazine has been shown to block evoked potentials at the entrances to the RF, but not to affect the onset of EEG desynchronization during direct stimulation of RF.

The earlier and deeper depression of the evoked potentials by cyclopropane than by chlorpromazine [6] or ether [2] can be considered to lead to the development of an afferent block of this structure. As a result, some depression of the RF develops, not because of the direct sensitivity of the reticular neurons to the action of cyclopropane, but through the development of an "excitation deficit" [4]. This hypothesis is in good agreement with the character of onset of desynchronization in stage II–III of general anesthesia. As was described above, stimulation of RF at constant intensity evokes slowly developing changes in the EEG, attaining the level of marked desynchronization only 1-3 sec after the beginning of stimulation. After the end of stimulation the EEG changes take place in the reverse order, and also gradually. This character of the changes, unlike desynchronization of the EEG during ether anesthesia, and coinciding exactly in time with the period of RF stimulation [2], confirms the view that the RF is exposed to an "excitation deficit"

as a result of the total blocking of afferent impulses, and is not depressed directly by the cyclopropane. Evidence of the integrity of the effector functions of the RF is given by the increase in activity of the sympathetic nervous system during cyclopropane anesthesia [15].

It is more difficult to interpret the results obtained on investigation of the TCR. The view that the positive wave of the TCR is associated with activity of presynaptic terminals [7] is difficult to accept, because discharges from the bodies of the neurons and, even more from their axons can hardly play an essential role in the formation of global electrical activity recorded from the cortical surface [1, 13]. The hypothesis of the participation of different populations of neurons in the formation of the positive and negative waves of the TCR [9] appears more convincing. In accordance with this hypothesis, the decrease in amplitude of this negative wave, associated with activity of the more superficial neurons, probably reflects depression of this group of neurons by cyclopropane. Because of the absence of experimental evidence of the direct facilitatory effect of general anesthetics during comparatively deep anesthesia in the literature, it is evident that the increase in amplitude of the positive wave was connected with a decrease in the subsequent negative wave; since these two waves undergo algebraic summation, in the waking animal the negativity arising before the end of the positivity cuts this wave short. It can therefore be postulated that depression of the negative wave during the action of cyclopropane "unmasks" the preceding positivity, increasing its amplitude. It can be concluded from these results that the general anesthesia produced by cyclopropane is not the result of depression of the nonspecific activating system of the brain stem. Selective depression of particular populations of cortical neurons in the association area of the cortex, together with the marked depression of responses in the cortical projection zone described in the literature [14] suggests that a primary disturbance of cortical function may play an important role in the development of cyclopropane anesthesia.

LITERATURE CITED

1. K. Yu. Bogdanov and V. B. Golovchinskii, Biofizika, No. 3, 530 (1969).
2. V. B. Golovchinskii and S. I. Plekhotkina, Zh. Vyssh. Nervn. Deyat., No. 6, 1277 (1970).
3. S. I. Plekhotkina, Byull. Éksperim. Biol. i Med., No. 8, 56 (1970).
4. G. N. Sorokhtin, Responses of Excitable Systems to an Excitation Deficit [in Russian], Moscow (1968).
5. J. F. Artusio, J. Pharmacol. Exp. Ther., 3, 343 (1954).
6. F. B. Bradley, in: The Reticular Formation of the Brain [Russian translation], Moscow (1962), p. 119.
7. H. T. Chang, J. Neurophysiol., 16, 117 (1953).
8. S. J. Goodman and P. E. G. Mann, Exp. Neurol., 19, 11 (1967).
9. B. Grafstein, J. Neurophysiol., 22, 504 (1959).
10. A. R. Guedel, Inhalation Anesthesia, New York (1938).
11. H. S. Davis, W. F. Collins, C. T. Randt, et al., Anesthesiology, 18, 634 (1957).
12. J. D. French, M. Verzeano, and H. W. Magoun, Arch. Neurol. Psychiat., 69, 505 (1953).
13. D. R. Humphrey, Electroenceph. Clin. Neurophysiol., 25, 421 (1968).
14. L. M. Kitahata, Wakayema Med. Rep., 5, 47 (1960).
15. R. A. Millar and T. J. Biscoe, Brit. J. Anaesth., 11, 804 (1965).
16. G. Moruzzi and H. W. Magoun, Electroenceph. Clin. Neurophysiol., 1, 455 (1949).
17. C. T. Randt, W. F. Collins, H. S. Davis, et al., Am. J. Physiol., 192, 305 (1958).