# ACTION OF ACETYLCHOLINE AND CARBACHOL WHEN INJECTED INTO THE CEREBRAL VENTRICLES

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Certain substances are known to have different, and sometimes opposite, actions when administered in the blood stream and cerebrospinal fluid. In experiments on dogs, G. N. Kassil' [2] showed that injection of carbachol into the cisterna cerebelli causes a marked sympathetic reaction: a rise of blood pressure, tachycardia, general excitation, and changes in the ECG. Differences in the effects of cholinomimetic drugs on the animal's behavior and on the EEG when administered by different methods have also been reported [5-8, 11-13].

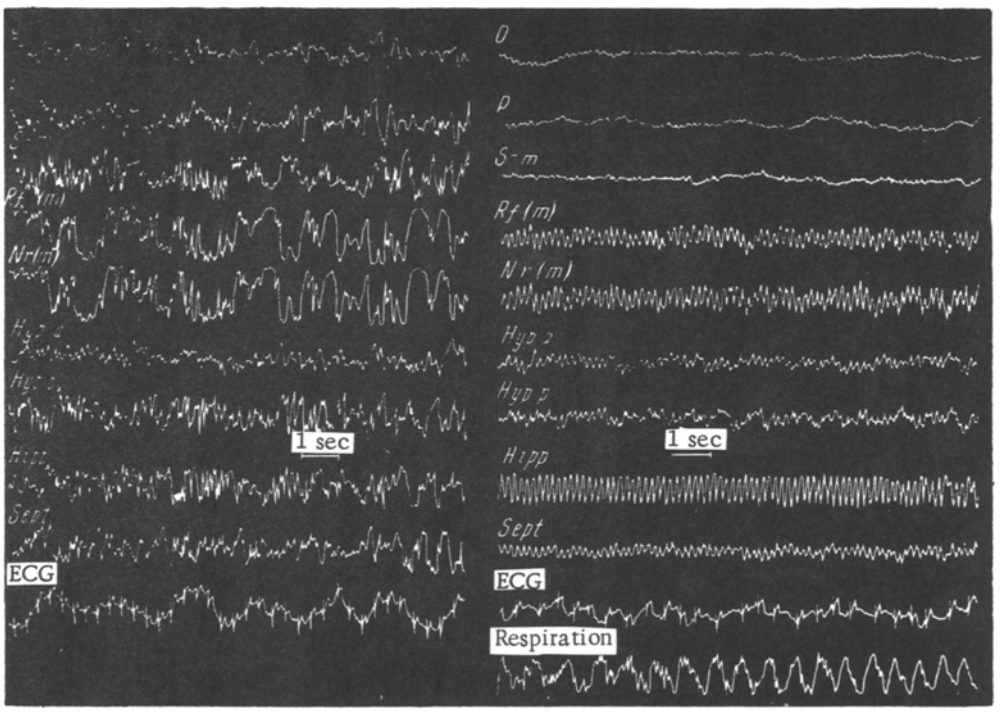


Fig. 1. Changes in electrical activity of a rabbit's brain after injection of 20 μg carbachol into the lateral ventricle. On the left) EEG before injection, on the right) after injection of carbachol; O) occipital region; P) parietal; S-M) sensorimotor; R.f.) reticular formation of mesencephalon; N.r.) nucleus reticularis of thalamus; Hyp.a.) anterior hypothalamic region; Hyp. p.) posterior hypothalamic region; Hipp) hippocampus; Sept) septum pellucidium; (m) unipolar.

The investigation of the effects of the intraventricular injection of cholinomimetric drugs, thereby circumventing the blood-brain barrier, and their comparison with the effects of intravenous injection of the same substances, may help in the study of the role of acetylcholine in the central nervous system. We have conducted long-term ex-

periments to study the changes in the EEG, the behavior, and certain autonomic indices after injection of acetylcholine and its stable homolog carbachol into the lateral ventricle of the rabbit's brain.

## EXPERIMENTAL METHOD

Experiments were conducted on rabbits with implanted electrodes. Recordings were made of the activity of the sensorimotor, parietal, and occipital regions of the cortex, the hippocampus, the septal region, the anterior and posterior regions of the hypothalamus, and the reticular formation of the mesencephalon. To introduce the test drugs into the lateral ventricle, a cannula was implanted. Experiments were started 8-10 days after the operation and repeated on the average once per week. The animals were preliminarily acclimatized to the experimental environment. The brain potentials, respiration, and pulse were recorded on an Alvar 15-channel encephalograph. Besides the spontaneous EEG, in a number of experiments the reaction of the rhythm to driving by flashes of light was investigated. For observations to be made on their behavior, the rabbits were placed in a transparent box. The head was brought out through a narrow aperture in the anterior wall, so that the animal's head movements were limited while the trunk and limbs were relatively free to move. The test drugs were injected into the lateral ventricle in 0.1-0.2 ml of physiological saline. Control experiments showed that the injection of physiological saline into the ventricle does not cause changes in the EEG or the autonomic indices and does not affect behavior. In some experiments the drugs were injected into the ventricle by means of a remote control system to exclude the possible influence of the procedure. Altogether 90 experiments were performed on 30 animals.

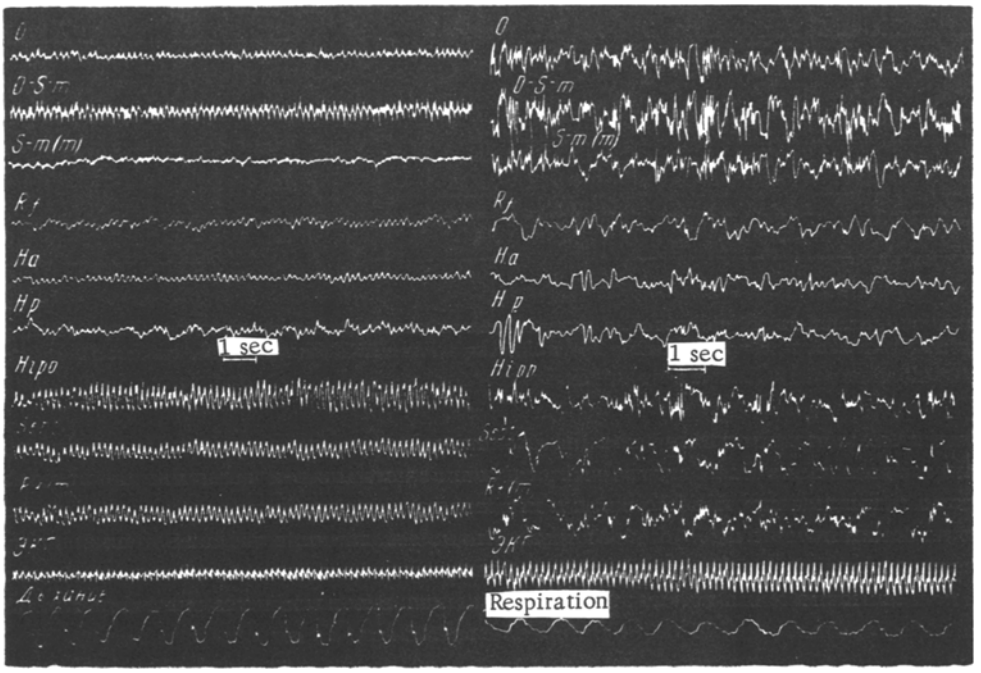


Fig. 2. Effect of injection of antrenyl (on left) and amizil (on right) on changes in the EEG of a rabbit caused by injection of carbachol into the lateral ventricle. Legend as in Fig. 1.

## EXPERIMENTAL RESULTS

The resting EEG of the rabbit has frequently been described [1, 3, 9, 12]. Our findings agreed with these observations.

Immediately after injection of acetylcholine from a dose of 5 μg and of carbachol from a dose of 1 μg, an arousal reaction appeared in the EEG. In the deep leads a clear, desynchronized rhythm of 5-7/sec developed, and in the neocortex a low-amplitude high-frequency activity appeared (desynchronization), against the background of which a synchronized rhythm of 5-7/sec was recorded in the occipital region (Fig. 1). With minimal doses of the drugs injected, the activation of the EEG lasted for 30 min. An increase in the dose of acetylcholine and carbachol increased the duration of activation without affecting its character. In some experiments convulsive discharges appeared in the EEG.

Marked and characteristic changes in behavior developed after injection of 10-20 μg carbachol or 50 μg acetylcholine. Immediately after injection of the drug the rabbit momentarily stood still as if listening to something; then, every 3-4 sec, almost rhythmic movements of the head from side to side were observed. Periodically a generalized motor excitation developed: the rabbit struck against the wall of the box, tried to bite it, shook itself, and kicked with its hind limbs. This state lasted for 15-20 min and then gradually subsided. When carbachol was given in a dose of 20 μg or more, 30-40 min after the beginning of the experiment excitation gave way to a depression of motor activity: the muscle tone diminished, ataxia appeared, and the rabbit sat on the floor of the box or lay motionless; its limbs could be placed for some time in an awkward position without resistance by the animal. The rabbit failed to react, or reacted weakly, to sharp stimuli such as a prick; at the same time it would try to run or to hide in a dark corner for no apparent reason. After 2-3 h the animal's behavior was indistinguishable from normal.

In most experiments acetylcholine and carbachol, when injected into the ventricle, caused an increase in the respiration rate, a slowing of the pulse (sometimes to ½ or ⅓ its original rate), and arrhythmia. In 9 of the 40 experiments the pulse rate was increased and in a few cases the respiration was slowed. In more than half the experiments, 0.5-2 min after injection of the test drugs a marked exophthalmos developed. Changes in the pupil were not recorded in every experiment: sometimes the pupil was dilated, sometimes constricted. Salivation was observed in nearly all the experiments.

Intravenous injection of the peripheral cholinolytic drug Antrenyl (oxyphenonium bromide) in a dose of 2-5 mg/kg had no effect on the excitation of the animals and activation of the EEG (Fig. 2) caused by acetylcholine and carbachol, although it completely suppressed the peripheral parasympathetic changes. Intravenous injection of the central muscarine-like cholinolytic drugs amizil (1-2 mg/kg) and atropine (3-10 mg/kg) completely suppressed or prevented the activation of the EEG caused by intraventricular injection of acetylcholine and carbachol but had no effect on the excitation of the animals (see Fig. 2).

Carbachol in doses of between 5 and 200 μg, and acetylcholine in doses of 200-400 μg, when injected intravenously caused no changes in the background electrical activity of the brain. Marked parasympathetic changes developed: a sharp decrease in the pulse rate and arrhythmia, constriction of the pupil, profuse salivation. Sometimes urination, defecation, and a lowering of muscle tone were observed.

The results show that the activating influence of the cholinomimetic drugs on the EEG is due to their direct action on the cholinergic elements of the central nervous system. The central effects of the cholinomimetic substances tested also include exophthalmos and dilatation of the pupils. In this respect our results confirm the earlier findings of sympathetic effects after injection of parasympatheticomimetic drugs into the cerebrospinal fluid. These observations clash with those reported by workers who found states resembling sleep, or stupor after injecting acetylcholine into the cerebral ventricles. It is difficult to analyze these differences because neither the test object nor the method used was the same. It is worth noting that John and co-workers [11] described the appearance of motor excitation in cats after injection of eserine into a cerebral ventricle and stressed the discrepancy between their findings and those of Feldberg, Dikshit, and others. MacLean also observed excitation in rabbits after administration of carbachol into the cerebrospinal fluid [13].

## SUMMARY

Acetylcholine (5-50 μg) and carbocholine (1-40 μg) administered into the lateral ventricle of the rabbit brain caused a distinct, stable picture of activation of the EEG, excitation and in a number of cases exophthalmos and bradycardia. The EEG activation was depressed and prevented by intravenous injection of central cholinolytics—amizil and atropine and remained unchanged after intravenous administration of peripheral cholinolytic—antrenyl. Not all the mentioned cholinolytics cause changes in the animals behavior. The presence of cholinergic synapses in structures having some relation to the activation reaction was confirmed.

## LITERATURE CITED

1. P. I. Kalinin and A. A. Sokolova, Fiziol. zh. SSSR, 5, 535 (1961).
2. G. N. Kassil', Byull. éksper. biol., 27, 2, 108 (1949).
3. L. A. Novikova and D. A. Farber, Abstracts of Proceedings of a Conference on the Electrophysiology of the Central Nervous System [in Russian], p. 91, Moscow (1958).
4. L. S. Shtern, Fiziol. zh. SSSR, 5, 577 (1946).
5. P. B. Bradley and J. Elkes, J. Brain, 80, p. 77 (1957).

6. P. M. Cooke and S.L. Sherwood, Electroenceph. clin. Neurophysiol., 6, p. 425 (1954).
7. B. B. Dikshit, J. Physiol. (London), 83, p. 42P (1935).
8. W. Feldber and S. L. Sherwood, Ibid., 125, p. 488 (1954).
9. J. D. Green and A. Arduini, J. Neurophysiol., 17, p. 533 (1954).
10. W. R. Henderson and W. C. Wilson, Quart. J. exp. Physiol., 26, p. 83 (1936).
11. E. R. John, B. M. Wenzel, and R. D. Tschirgi, J. Pharmacol. exp. Ther., 123, p. 193 (1958).
12. V. G. Longo, et al., Ibid., III, p. 349 (1954).
13. P. D. MacLean, J. Neurosurg., II, p. 29 (1954).

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**All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal.** ***Some or all of this periodical literature may well be available in English translation.*** **A complete list of the cover-to-cover English translations appears at the back of this issue.**