COMPARATIVE NATURE OF THE INFLUENCE OF N- AND M-CHOLINOLYTIC SUBSTANCES ON THE BIOEL' CTRIC ACTIVITY OF THE BRAIN

(UDC 615.784-092 : 612.822.3.087 + 612.822.3.087-064 : 615.784)

O. G. Baklavadzhyan

Laboratory of the Development of the Vegetative Nervous System (Director—Candidate of Biological Sciences, O. G. Baklavadzhyan), Academician L. A. Orbeli Institute of Physiology Armenian SSR Academy of Sciences, Erevan
(Presented by Member of the Academy of Sciences USSR, S. V. Anichkov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 59, No. 2, pp. 70-75, February, 1965
Original article submitted October 10, 1963

According to the data of S. V. Anichkov and colleagues [3], there are two types of cholinoreceptors in the central and peripheral nervous system: one of these is sensitive to the nicotine-like action of acetylcholine (N-cholinoreceptors), and the other is sensitive to the muscarine-like action of acetylcholine (M-cholinoreceptors).

In order to determine the mechanism of the action of certain central cholinolytics with selective N- and M-cholinolytic action and for the determination of the type of cholinoreceptor structures of the reticular formation of the mesencephalon and the cerebral cortex, in this work we studied the action of the cholinolytics gangleron, arpenal, and atropine on the EEG of the cortex and reticular formation of the mesencephalon. Gangleron selectively blocks the nicotine-sensitive cholinergic synapses of the central nervous system [1, 10], arpenal—both the N- and M-cholinoreceptive systems of the brain, chiefly the N-cholinolytic action [2, 11]. Atropine is known as a selective M-cholinolytic.

PROCEDURE

Acute experiments were carried out on 45 female cats, nonanesthetized* with prokuran. The influence of an intraveneous administration of N- and M-cholinolytics on the EEG of the cortex and reticular formation and on the "recruiting" reaction, caused by a low frequency (six cycles per second) stimulation of the nonspecific nucleus of the thalamus (nucl. ventralis anterior), was investigated. The influence of the indicated preparations on the EEG was also studied on cats in the waking state, using permanently implanted multiple electrodes.

In a special series of experiments, the influence of the local application of the preparations on the primary and secondary cortical responses induced by the stimulation of the sciatic nerve, were investigated.

RESULTS OF THE EXPERIMENTS

In curarized cats under the conditions of an acute experiment without narcosis, waves of medium amplitude (30-100 μV) with a frequency of 4-10 per second predominate on the background EEG. Sometimes such an initial activity alternates with periodic activation in the form of spontaneous desynchronization with the appearance of low-amplitude, high-frequency oscillation potentials. In a number of cases, constant desynchronization is observed on the initial EEG of the cortex and reticular formation. Electrical stimulation of the sciatic nerve, as well as stimulation of the reticular formation of the mesencephalon by impulses with a frequency of 200 cycles per second causes a prolonged activation of the brain with a desynchronization type of reaction, which was expressed in the appearance of a low-amplitude high-frequency activity on the EEG of the resting cortex and reticular formation (Fig. 1, 1).

The intravenous administration of a dose of 4 mg/kg of gangleron causes the appearance of slow waves on the EEG during the first 3-5 min. Since these changes in the EEG take place against a background of a considerable drop in arterial pressure, they are probably a reflection of disruption of the brain circulation. After the normalization of the blood pressure, the slow waves disappear, the initial EEG is reestablished, and afferent stimulation causes the

*Publisher's note: Possible Russian misprint.

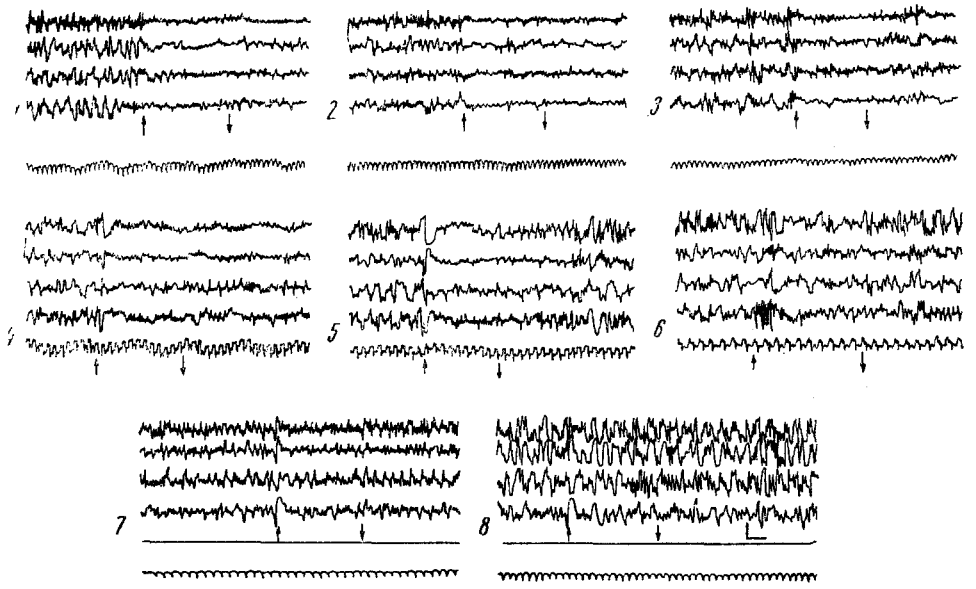

Fig. 1. Influence of N- and M-cholinolytics on the activation of the EEG of the cortex and reticular formation of the mesencephalon caused by electrical stimulation of the sciatic serve. The results of three acute experiments are cited (1-3, 4-6, 7-8). Significance of the curves (from top to bottom): EEG of the frontal, parietal, and occipital regions of the cerebral cortex and the reticular formation of the mesencephalon; ECG. 1) Control recording; 2) 10 min after the administration of 4 mg/kg of gangleron; 3) 10 min after an additional administration of 5 mg/kg gangleron (total dose 9 mg/kg); 4) control recording of another experiment; 5) 12 min after the administration of arpenal; 6) 15 min after the additional administration of 5 mg/kg of arpenal (total dose 9 mg/kg); 7) control recording of a third experiment; 8) 10 min after the administration of a dose of 1.5 mg/kg of atropine. The beginning and end of the administration of the preparation are indicated by arrows. Explanations in text.

same desynchronization as before the administration of the preparation (Fig. 1, 2). An additional administration of gangleron at a dose of 5 mg/kg causes the same effect. Sometimes a small disturbance in the "recruiting" reaction is recorded—the stimulation threshold of the sciatic nerve under these conditions causes a less pronounced desynchronization, of shorter duration compared with the norm (Fig. 1, 3). In spite of the fact that during the experiment the total dose of gangleron approaches 9-10 mg/kg, the ascending activating system of the reticular formation is not blocked by the N-cholinolytic. This is also observed in chronic experiments during intramuscular administration of gangleron at a dose of 10 mg/kg.

Arpenal (N-M-cholinolytic substance) at the same dosages causes more pronounced changes in the bioelectric activity of the cortex and reticular formation. The intraveneous administration of arpenal in a dosage of 4 mg/kg is accompanied by the appearance of a slow wave with a high amplitude both in the cortex and in the reticular formation (Fig. 1, 5). During electrical stimulation of the sciatic nerve or reticular formation of the mesencephalon a sharp desynchronization reaction arises, which, however, takes place only at the moment of actual stimulation. The additional administration of arpenal at a dose of 5 mg/kg usually causes complete blockage of the desynchronization reaction to a peripheral stimulation (Fig. 1, 6), and even electrical stimulation of the reticular formation sometimes does not cause activation of the EEG. The same effect is exhibited by the administration of arpenal in chronic experiments.

Atropine causes still more pronounced changes in the EEG. During the intraveneous administration of atropine in a dose of 1-2 mg/kg, slow waves (1-3 per second) with a large amplitude (100-300 microvolts) appeared on the EEG of the cortex and reticular formation, and were not suppressed during subthreshold electrical stimulation of the peripheral nerves (Fig. 1, 8) and the reticular formation of the mesencephalon.

Thus, the use of cholinolytic preparations with selective N- and M-cholinolytic action provided the possibility

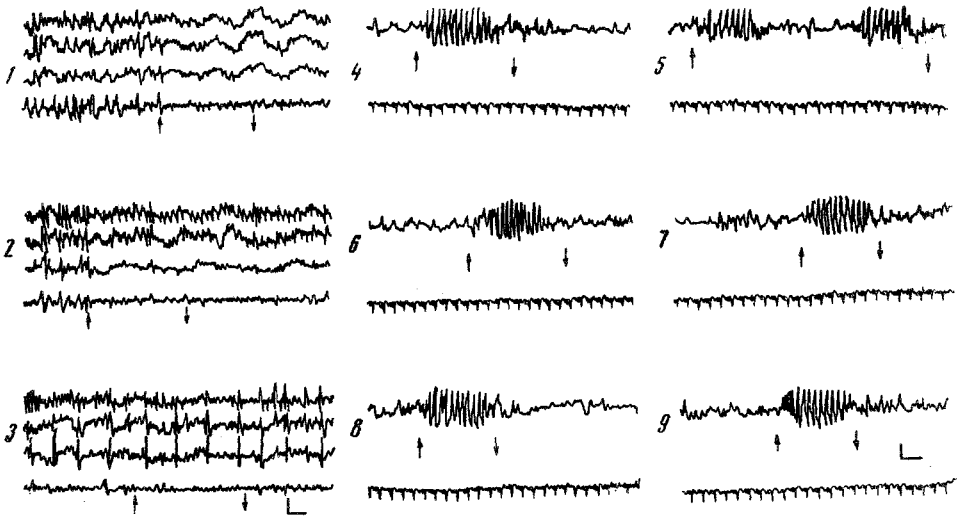

Fig. 2. Influence of a local application of the cholinolytics on the electrocorticogram (1-3). Meaning of the curves (from top to bottom): EEG of the left frontal, left parietal, left occipital, and right parietal lobes of the cortex. 1) Control recording of EEG and "recruiting" reaction during the stimulation of the sciatic nerve; 2) 2 min after a four minute local application of gangleron (frontal lobe), arpenal (parietal lobe), and atropine (occipital lobe); 3) 10 min after a secondary application of the preparations, influence of N- and M-cholinolytics on the "recruiting" reaction; 4) control recording; 5) 20 min after an intramuscular application of gangleron at a dose of 10 mg/kg; 6) control recording; 7) 25 min after intramuscular administration of arpenal at a dose of 10 mg/kg; 8) control recording; 9) 30 min after intramuscular administration of atropine at a dose of 10 mg/kg.

for showing qualitative differences in their action on the electric activity of the brain. In the series gangleron—arpenal—atropine, the action on the EEG increased as the muscarinolytic action of the preparation increased. Consequently, it may be assumed that in an activating system of the reticular formation of the mesencephalon M-cholinoreactive structures predominate.

Does a qualitative difference exist in the action of N- and M-cholinolytics on the diffuse, nonspecific structures of the thalamus, which exert a primary influence on the associative cortex? From the literature data [1, 9] it is known that atropine does not suppress the "recruiting" reaction caused by a low-frequency stimulation of the nonspecific nuclei of the thalamus (Fig. 2, 9). We established that the nonspecific structures of the activation phase of the brain possess low sensitivity to the action of not only M- but also N-cholinolytics. Gangleron and arpenal in an intramuscular dose of 10 mg/kg do not noticeably change the "recruiting" reaction, both during their independent use in individual experiments and during a combined sequential use of them in the same experiments (Fig. 2, 5, 7). Consequently, it should be assumed that cholinolytic substances of any type do not inhibit the nonspecific thalamocortical afferentation.

In order to explain the sensitivity of the cortical synapses to the action of both anticholinergic preparations of N-, and M-, cholinolytic types, the influence of the local application of gangleron, arpenal and atropine on the electrocorticogram and the induced potentials of the cortex were studied in a special series of experiments. It was established that the application of these preparations on the surface of the cortex causes the appearance of slow waves on the EEG only in the region of application while the bioelectric activity drawn off from the neighboring control region, continued to remain normal. The slow waves were most pronounced in the zones in which gangleron and arpenal were applied (Fig. 2, 2). A considerable inhibition of the desynchronization reaction was observed in these regions. The repeated use of the preparations inhibited the desynchronization reaction in the zones of atropine application as well. In this region 10-15 min after application, spontaneous high amplitude strychnine-like commissures, arising regularly once each 1.5-2 sec, were recorded (Fig. 2, 3).

The data of these experiments give a basis for the assumption that the cortical surface structures are sensitive to the reaction of N- and M- cholinolytic substances, and also that there is a qualitative difference in the action of

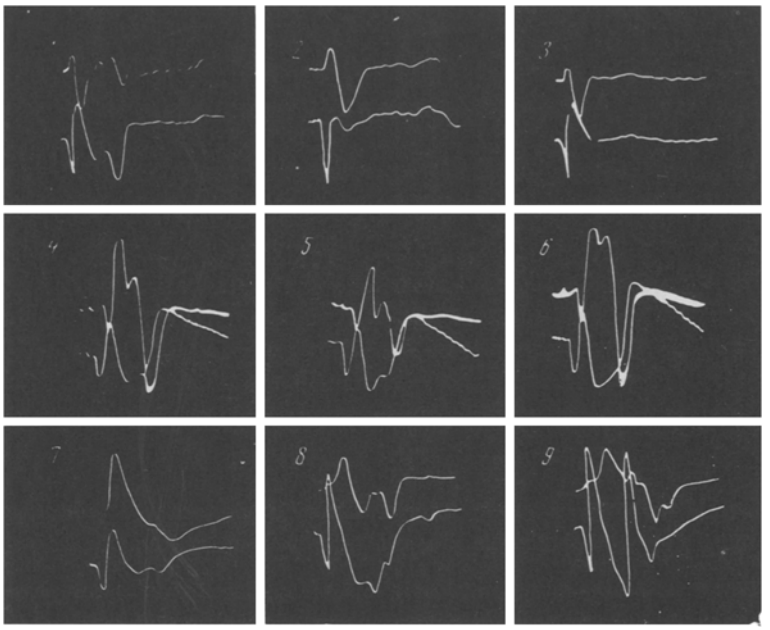

Fig. 3. Influence of local application of N- and M-cholinolytics on the primary responses of the second somatosensory zone of the cortex, caused by a single electrical stimulation of the sciatic nerve. Application of the preparation was performed in the zone of primary responses. Cited are the results of three experiments. In all the oscillograms: upper curve—secondary response in gyr. Lateralis anterior; lower curve—primary response in gyr. Ectosylvius anterior; 1) control recording; 2) after gangleron application; 3) restoration after washing cortex with physiological solution; 4) control recording; 5) after arpenal application; 6) restoration; 7) control recording; 8) after atropine application; 9) after washing with physiological solution. Upward deflection of beam—negative oscillation. Time marker is 10 sec. Rate of increase was 100 μV.

N- and M-cholinolytics of the cortical synapses. These data were confirmed in experiments where the induced potentials were recorded. The influence of local application of gangleron, arpenal, and atropine was studied, both during their individual application in various experimenta and during sequential application of them in the same experiment. The results were uniform in all the experiments. Local application of a 1.5% solution of gangleron in the zone of primary responses causes an inhibition of the negative phase of the primary response and an increase in the positive (Fig. 3, 2). The effect of gangleron is somewhat like the effect of γ-aminobutyric acid, which according to certain authors [20] selectively blocks the axodendritic stimulation of the synapses of the cerebral cortex.

In a series of experiments studying the effect of local application of arpenal (Fig. 3), it was established that the inhibition of the negative phase of the induced potential under the influence of arpenal was less pronounced in comparison with the effect of gangleron (Fig. 3, 5). Atropine has an effect directly opposite to that of gangleron. Under the action of atropine, a gradual increase in the negative potential takes place; the "atropine" potential (with a pronounced negative peak, sometimes going off the oscillograph screen) is similar to the strychnine potential (Fig. 3, 8, 9). An increase in the negative phase of the primary response under the influence of atropine is explained [17] by the presence of inhibiting hyperpolarizing synapses in the cortex, sensitive to atropine. In the interpretation of the action of gangleron and atropine on the induced potentials, we proceed from the assumption that the surface-negative wave of the primary response is a post-synaptic dendritic potential [12, 21], while action on it by the cholinolytic preparations that we used, we considered as the influence of stimulating, depolarizing, and inhibiting, hyperpolarizing axodendritic synapses. Evidently the cortical synapses of different electrogenesis (stimulating and inhibiting) manifest a different sensitivity to N- and M- cholinolytic substances. In the cerebral cortex there are probably both N- and M-cholinoreactive structures with a predominance, evidently, of N-cholinoreceptors in the stimulating axodendritic synapses of the cortex.

LITERATURE CITED

1. N. E. Akopyan, In the Book: Gangleron and Experience in Its Clinical Use [in Russian], Erevan, (1959), p. 51.
2. N. E. Akopyan, In the Book: Arpenal and Experience in Its Clinical Use [in Russian], Erevan, (1964), p. 57.
3. S. V. Anichkov and M. A. Grebenkina, Byull. Eksper. Biol. No. 9, (1957), p. 28.
4. N. N. Anosov, Nevropatol. i Psikhiatr., 2, (1962), p. 223.
5. P. K. Anokhin, Zh. Vyshch. Nervn. Deyat., 4, (1959), p. 489.
6. P. P. Denisenko, Fiziol. Zh. SSR, No. 2, (1962), p. 160.
7. P. P. Denisenko, Farmakol. i Toksikol., No. 1, (1962), p. 8.
8. P. P. Denisenko, In the Book: Pharmacology of New Sedative Agents and Their Clinical Application. Leningrad, (1962), p. 107.
9. R. Yu. Il'yuchenok and R. U. Ostrovskaya, Byull. Éksper. Biol. No. 7, (1962), p. 43
10. M. Ya. Mikhel'son, In the Book: Gangleron and Experience in its Clinical Application. Erevan, (1959), p. 128.
11. M. Ya. Mikhel'son, et al. In the Book: Arpenal and Experience in Its Clinical Application. Erevan, (1964), p. 76.
12. A. I. Roitbak, Bioelectric Phenomena in the Cerebral Cortex [in Russian], Tbilisi, (1955).
13. G. D. Smirnov and R. Yu. Il'yuchenok, Fiziol. Zh. SSSR, No. 10, (1962), p. 1141.
14. M. Bonvallet, P. Dell, and G. Hiebel, Electroenceph. clin. Neurophysiol., 6, (1954), p. 119.
15. P. B. Bradley, In Book: Reticular Formation of the Brain, London, (1957), p. 123.
16. P. B. Bradley and J. Elkes, Brain, 80, (1957), p. 77.
17. P. O. Chatfield and D. P. Purpura, Electroenceph. clin. Neurophysiol., 6, (1954), p. 287.
18. V. G. Longo, Experientia, (Basel), 11, (1955), p. 76.
19. Idem, Electroencephalographic Atlas for Pharmacological Research. Amsterdam, (1962).
20. D. P. Purpura and H. J. Grundfest, Neurophysiol., 19, (1956), p. 573.
21. D. P. Purpura, M. Girado, and H. Grundfest, Science, 125, (1957), p. 1200.
22. F. Rinaldi and H. E. Himwich, Arch. Neurol. Psychiat, 73, (1955), p. 387.
23. A. B. Rothballer, Electroenceph. clin. Neurophysiol., 8, (1956), p. 603.
24. M. J. Vogt, Physiol. (Lond.). 123, (1954), p. 451.

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.
