ROLE OF CHOLINERGIC ELEMENTS OF THE ASCENDING RETICULAR ACTIVATING SYSTEM IN BLOCKING OF THE ADRENERGIC ELECTROENCEPHALOGRAPHIC ACTIVATION REACTION BY CHOLINOLYTICS

Yu. F. Pastukhov

UDC 612.822.3.014.6:615.217.34

The widely held view that the ascending reticular activating system (ARAS) is adrenergic in nature is disputed by a number of writers [12, 14, 15] because of the existence of cholinergic structures in this system. Recent experiments have yielded results indicating, on the one hand, that the ARAS at the brain stem level is chemically heterogeneous [2, 6], and on the other hand, that the terminal neuron of the ARAS in the cortex, participating in the electroencephalographic (EEG) activation reaction is chemically homogeneous (cholinergic) [9]. Meanwhile it has been stated that amphetamine, administered against the background of blocking of the central cholinergic structures by atropine, does not induce an EEG activation reaction [10, 13, 15].

These observations call for a more detailed study of the role of the cholinergic structures of the ARAS in the mechanism of blocking of the adrenergic EEG activation reaction by cholinolytics.

EXPERIMENTAL METHOD

Changes in electrical activity of various areas of the cortex, the nonspecific nuclei of the thalamus, and the mesencephalic reticular formation were investigated in 95 animals: in waking rabbits in chronic experimental conditions and in cats with an intact brain and after transsection of the brain stem in acute experimental conditions.

The operations were performed under ether anesthesia; at the end of anesthesia the cats with an intact brain were immobilized with the curare-like agent displacin and transferred to artificial respiration. The brain was divided mechanically and electrolytically: at the level of the trigeminal nerve nuclei (trigeminal sections), through the rostral part of the pons, and through the mesencephalon (mesencephalic sections). Simultaneous recordings were made of the background bioelectrical activity and of changes in the EEG in response to rhythmic flashes of different frequencies (the "following" response), to acoustic stimulation, and to electrical stimulation (rectangular pulses, 250-300 cps, duration 0.5 msec) of the sciatic nerve or mesencephalic reticular formation (arousal response).

To produce pharmacological excitation of the adrenergic structures of the ARAS, in addition to amphetamine the central adrenomimetic drug pipradrol [4] was used. The latter is similar in its action to amphetamine but differs from it in its peripheral sympathomimetic effect [11]. To study the mechanism of blocking of the adrenergic EEG activation reaction a number of different cholinolytic drugs possessing a blocking action on both central and peripheral muscarine-like (M) and nicotine-like (N) cholinergic structures were used. All drugs investigated were injected intravenously.

EXPERIMENTAL RESULTS

Experiments on animals with an intact brain showed that, against the background of a clearly defined EEG activation reaction evoked by pipradrol or amphetamine (5 mg/kg), administration of even small doses of the benzylic acid esters benactyzine, benzazine (2-dimethylaminoethylester of benzylic acid), and methamicil (methyldiazil) (beginning with 0.05-0.1 mg/kg), possessing a central M-cholinolytic action, abolished

Laboratory of Pharmacology, Department of Experimental Biology, Institute of Cytology and Genetics, Siberian Division, Academy of Sciences of the USSR, Novosibirsk (Presented by Active Member of the Academy of Medical Sciences of the USSR V. V. Zakusov). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 64, No. 12, pp. 55-59, December, 1967. Original article submitted December 30, 1965.

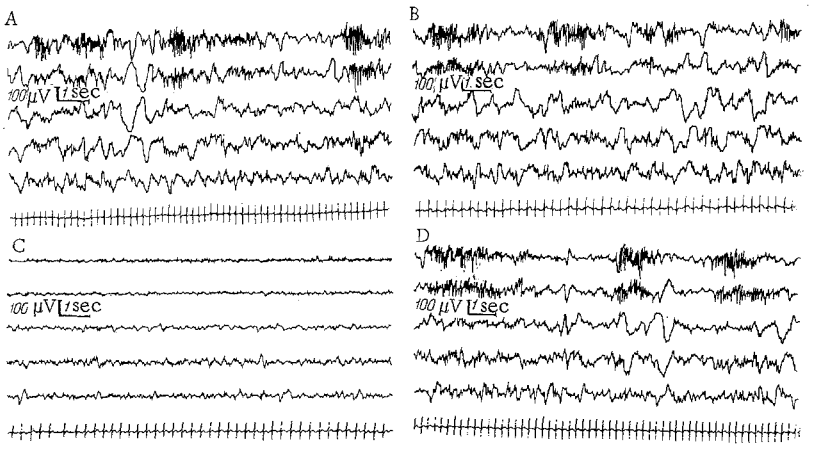

Fig. 1. Effect of gangleron, pipradrol, and benactyzine on electrical activity of different parts of the rabbit's brain. From top to bottom: EEG of sensorimotor areas of left and right hemisphere, reticular nucleus and centrum medianum of the thalamus, left mesencephalic reticular formation, ECG. A) Before injection; B) 10 min after intravenous injection of gangleron (10 mg/kg); C) 9 min after intravenous injection of pipradrol (3 mg/kg); D) 2 min after intravenous injection of benactyzine hydrochloride (0.3 mg/kg).

this activating effect and restored slow electrical activity in the cortex, in the peripheral nuclei of the thalamus, and in the mesencephalic reticular formation (Fig. 1D). With an increase in dose of the M-cholinolytic, changes in the background activity became more marked and persistent. At the same time the degree of blocking of the arousal response to acoustic and electrical stimulation increased. The improvement in the "following" response observed against the background of action of pipradrol and amphetamine likewise was abolished. The "following" response to rhythmic flashes of high frequency (16-50/sec) became even worse than before injection of the preparations. These M-cholinolytics gave a blocking action of about equal strength (the action of methamicil was a little stronger).

Atropine, which besides a powerful peripheral cholinolytic effect also has a well marked action on central M-cholinergic systems, blocked the pipradrol and amphetamine EEG activation reaction in much larger doses (starting from 2-3 mg/kg). This is in agreement with reports that the central M-cholinolytic action of atropine is weaker than that of benzylic acid esters [3].

The peripheral M-cholinolytic oxyphenonium bromide, in a dose of 0.4 mg/kg, had no action on the activating effect of pipradrol and amphetamine, whether administered before or after. The dose of oxyphenonium bromide used causes no changes in electrical activity of the brain [3], and is almost 100 times greater than the dose required to block peripheral M-cholinergic structures [7].

The results of these experiments demonstrate that abolition of the adrenergic EEG activation reaction by benzylic acid esters and atropine is associated with blocking of central M-cholinergic structures.

In the case of tropazine* and adiphenine hydrochloride, with the property of blocking N-cholinergic structures in small doses, and both M- and N-cholinergic structures in large doses [5, 6], these drugs blocked the adrenergic EEG activation reaction only when given in doses producing a central M-cholinolytic effect (not less than 2-3 mg tropazine and 3-6 mg adiphenine/kg; Fig. 2).

To prevent the activating effect of pipradrol and amphetamine, much higher doses of the central M-cholinolytic were required than to abolish it.

The use of a series of N-cholinolytics in this investigation made it possible to differentiate more closely between the role of M- and N-cholinergic structures in the mechanism of blocking of the adrenergic EEG activation reaction by cholinolytic drugs. Both N-cholinolytics with peripheral ganglion-blocking

*1,2-dimentyl-3-diethyl-aminopropyl-p-isobutoxybenzoate hydrochloride.

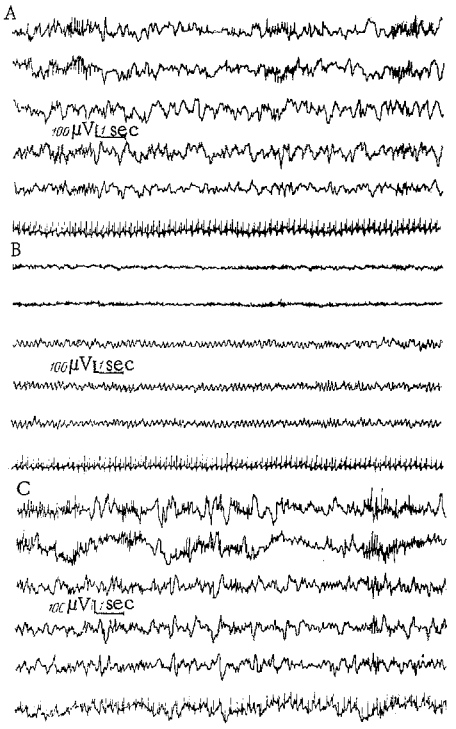

Fig. 2. EEG of various parts of the rabbit's brain during action of amphetamine and adeiphenine hydrochloride. From top to bottom: EEG of left and right sensorimotor cortex, of reticular nucleus and centrum medianum of thalamus, of left mesencephalic reticular formation, ECG. A) Before injection; B) 3 min after intravenous injection of amphetamine (5 mg/kg); C) 15 min after intravenous injection of adiphenine hydrochloride (13 mg/kg).

(hexamethonium) and curare-like (diplacin) action, and gangleron,* pachycarpine, and nanophyne,† possessing central N-cholinolytic action also [1], if injected intravenously sufficiently slowly (about 3 mg/kg/min) even in large doses (up to 10 mg/kg) had no significant action on the time of appearance, duration, and severity of the EEG activation reaction evoked by pipradrol and amphetamine (Fig. 1C), and had no effect likewise on the arousal and "following" responses.

Hence, experiments on animals with an intact brain demonstrated that the EEG activation reaction evoked by stimulation of adrenergic structures of the reticular formation by pipradrol and amphetamine may be abolished by blocking central M-cholinergic structures.

Relationships between the adrenomimetics and central M-cholinolytics retained the same character after transection of the brain stem, when pipradrol and amphetamine continued to evoke an EEG activation reaction (trigeminal and mesencephalic sections). With a decrease in the part of the mesencephalic reticular formation left in communication with higher brain structures, the activating action of the adrenomimetics was weakened, but the blocking of this action by central M-cholinolytics was facilitated.

However, the level of the ARAS at which this blocking took place remains unexplained. Unquestionable central M-cholinolytics produce blocking of M-cholinergic structures of the reticular formation of the brain stem and thereby suppress cholinergic activation. However, in these conditions an EEG activation reaction is observed during excitation of adrenergic reticular structures [2, 8]. Consequently, the adrenergic EEG activation reaction is blocked by M-cholinolytics somewhere in the higher regions of the brain. The results of experiments with local application of cholinolytic substances [9] show that the endings of the ascending pathways of the reticular activating system in the cerebral cortex are M-cholinergic: amphetamine activation is blocked in the region of application of the M-cholinolytic, while intravenous injection of anticholinesterase drugs removes this block.

On the basis of all these data it may be postulated that M-cholinergic cortical neurons of the ARAS are one place where mechanisms blocking the adrenergic EEG activation reaction by M-cholinolytics operate.

LITERATURE CITED

1. N. E. Akopyan, In the book: Gangleron and Clinical Experience of its Use [in Russian], Erevan (1959), p. 51.
2. R. Yu. Ilyuchenok, In the book: Proceedings of the First International Pharmacological Meeting: "Pharmacological Analysis of Central Nervous Action." New York, 8 (1962), p. 211.
3. R. Yu. Il'yuchenok and R. U. Ostrovskaya, Farmakol. i Toksikol., No. 6, 643 (1962).
4. R. Yu. Il'yuchenok and Yu. F. Pastukhov, Zh. Nevropat. Psikhiat., No. 12, 1821 (1962).
5. S. S. Liberman, Farmakol. i Toksikol., No. 6, 18 (1950).
6. M. D. Mashkovskii, Farmakol. i Toksikol., No. 5, 3 (1953).
7. M. D. Mashkovskii and S. S. Liberman, Farmakol. i Toksikol., No. 3, 216 (1959).

*2,3-Dihydro-3-hydroxy-8-methylnortropidine-diphenylacetate hydrochloride.
†2,6-Dimethylpiperidine hydrochloride.

8. Yu. F. Pastukhov, In the book: Collected Proceedings of the 3rd Scientific Conference of Physiologists, Biochemists, and Pharmacologists of the Western Siberian Union [in Russian], Tomsk (1965), p. 326.
9. G. D. Smirnov and R. Yu. Il'yuchenok, Fiziol. Zh. SSSR, No. 10, 1141 (1962).
10. P. B. Bradley and J. Elkes, Brain, 80, 77 (1957).
11. B. B. Brown and H. W. Werner, J. Pharmacol. exp. Ther., 110, 180 (1954).
12. K. A. Exley, M. K. Fleming and A. D. Espelien, Brit. J. Pharmacol., 13, 485 (1958).
13. V. G. Longo, EEG Atlas for Pharmacological Research. Amsterdam (1962).
14. F. Rinaldi and H. E. Himwich, Arch. Neurol. Psychiat., 73, 396 (1955).
15. R. P. White, Arch. int. Pharmacodyn., 145, 1 (1963).