EFFECT OF CHOLINERGIC SUBSTANCES ON BIOELECTRICAL ACTIVITY OF THE LIMBIC SYSTEM

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Injection of anticholinesterase (eserine, galanthamine) and cholinometic (arecoline, oxotremorine, nicotine) into intact rabbits leads to the appearance of a θ rhythm on the EEG of the hippocampus, septum pellucidum, the middle and posterior parts of the gyrus cinguli, the visual cortex, and the pontomesencephalic reticular formation. A fast, low-amplitude rhythm is recorded on the EEG of the sensorimotor cortex, the anterior part of the gyrus cinguli, and the amygdala. The EEG-activation response is blocked by benactyzine and by benzacine.

Premesencephalic section does not abolish the θ rhythm produced by anticholinesterase and cholinomimetic drugs in the structures of the limbic system and in the separated reticular formation, whereas slow low-amplitude waves persist in the neocortex. Destruction of the posterior hypothalamus associated with premesencephalic section prevents the genesis of a θ rhythm in the limbic system. An important role in the activity of the limbic system is ascribed to its intrinsic cholinergic mechanisms.

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Administration of anticholinesterase drugs leads to the appearance of a θ rhythm in the hippocampus [8, 9]. The reticular formation (RF) of the brain stem is considered to play an important role in the mechanism of these disturbances, together with the septum pellucidum [4, 7, 10].

The object of this investigation was to discover the relationship between changes in bioelectrical activity of the hippocampus and other structures of the limbic system and brain-stem RF mechanisms. For this purpose the action of cholinergic drugs was compared in animals with connections between the hippocampus and brain-stem RF intact and after premesencephalic section.

EXPERIMENTAL METHOD

Chronic and acute experiments were performed on 100 adult rabbits (2.8-3.8 kg). Under intravenous nembutal anesthesia bipolar nichrome electrodes covered with polyester varnish except at the tip (interelectrode distance 1 mm, diameter 0.22 mm) were implanted in the dorsal regions of both hippocampi, the septum pellucidum, the anterior, middle, and posterior parts of the gyrus cinguli, the amygdala, and brain-stem RF. Potentials of the sensorimotor and visual cortex were recorded with bipolar steel needles 0.5 mm in diameter, interelectrode distance 3 mm. The initial electroencephalogram (EEG) was recorded 5-6 days later and the action of the test drugs studied. One week later, under ether anesthesia, mechanical premesencephalic section was carried out on the same animals without disturbing the integrity of the hippocampi and neocortex. The EEG was recorded on a Kaiser ink-writing electroencephalograph.

After the end of the experiments the brain was fixed in 10% formalin solution and the position of the section and of the electrodes was verified morphologically.

EXPERIMENTAL RESULTS

After intravenous injection of anticholinesterase drugs – eserine (0.3 mg/kg) or galanthamine (3 mg/kg) – and also of cholinomimetics – arecoline (0.3 mg/kg; Fig. 1), nicotine (0.3 mg/kg), or oxotremorine (0.15 mg/kg) – into animals with an intact brain, an EEG-activation response appeared: a fast low-

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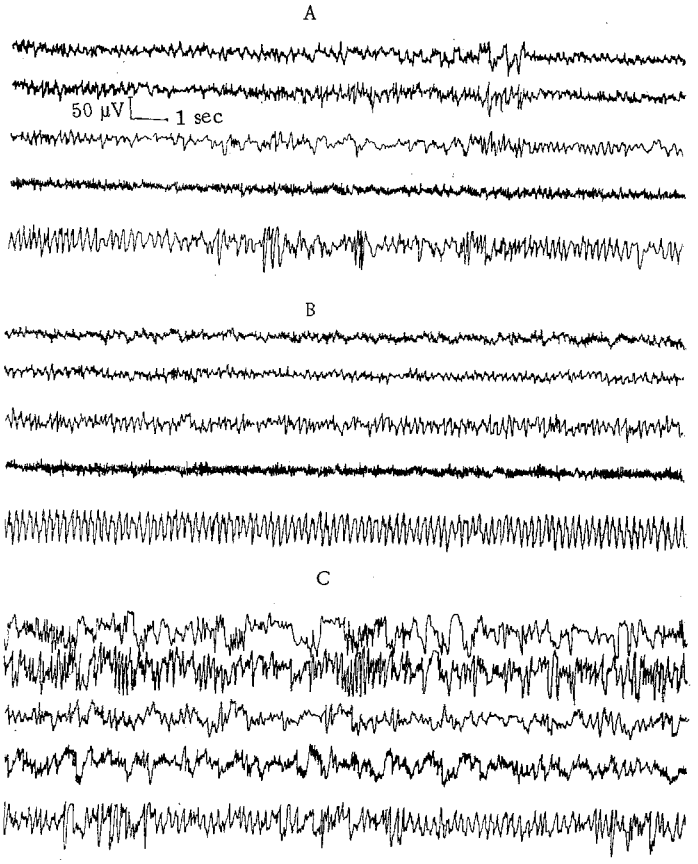

Fig. 1. Effect of arecoline on bioelectrical activity of structures of the limbic system in rabbits. From top to bottom: EEG of right sensorimotor cortex, middle parts of right gyrus cinguli, septum, right amygdala, right dorsal hippocampus. A) Before injection; B) 5 min after intravenous injection of arecoline (0.3 mg/kg); C) 5 min after intravenous injection of benzacine (2 mg/kg).

amplitude rhythm in the sensorimotor cortex, the anterior parts of the gyrus cinguli, and in the amygdala, together with a θ rhythm in the hippocampus, septum pellucidum, middle and posterior parts of the gyrus cinguli, visual cortex, and brain-stem RF. The action of these drugs on electrical activity of the neocortex and structures of the limbic system was blocked by intravenous injection of central muscarine-like anticholinergic drugs (M-cholinolytics): benactyzine in a dose of 0.6-1 mg/kg or benzacine (2-dimethylaminoethyl ester of benzilic acid hydrochloride) in a dose of 1-3 mg/kg. In this case, irregular slow waves of high amplitude appeared on the EEG both of the neocortex and of structures of the limbic system. Similar changes in bioelectrical activity in response to the action of anticholinergic drugs have been found also in animals without previous administration of anticholinesterase drugs [1, 2, 11].

After injection of cholinomimetics and anticholinesterase drugs in the same doses into animals with premesencephalic brain section, no EEG activation was observed in the neocortex, just as was previously found [3], while a regular rhythm of 4-6/sec was present in the separated pontomesencephalic RF (Fig. 2). So far as changes in the bioelectrical activity of the hippocampus and septum are concerned, after premesencephalic section a θ rhythm appeared in response to anticholinesterase (eserine and galanthamine) and cholinomimetic drugs (arecoline, oxotremorine, and nicotine) (Fig. 3).

Changes in the EEG in response to injection of these drugs, after complete exclusion of the RF, were also found in the amygdala in the form of a fast low-amplitude activity. The antagonistic blocking effect of M-cholinolytics was equally apparent in the animals with premesencephalic section as in those with an intact brain. At the same time, changes in the EEG of the gyrus cinguli following administration of anticholinesterase and cholinomimetic drugs were less marked than in animals with an intact brain (Fig. 2).

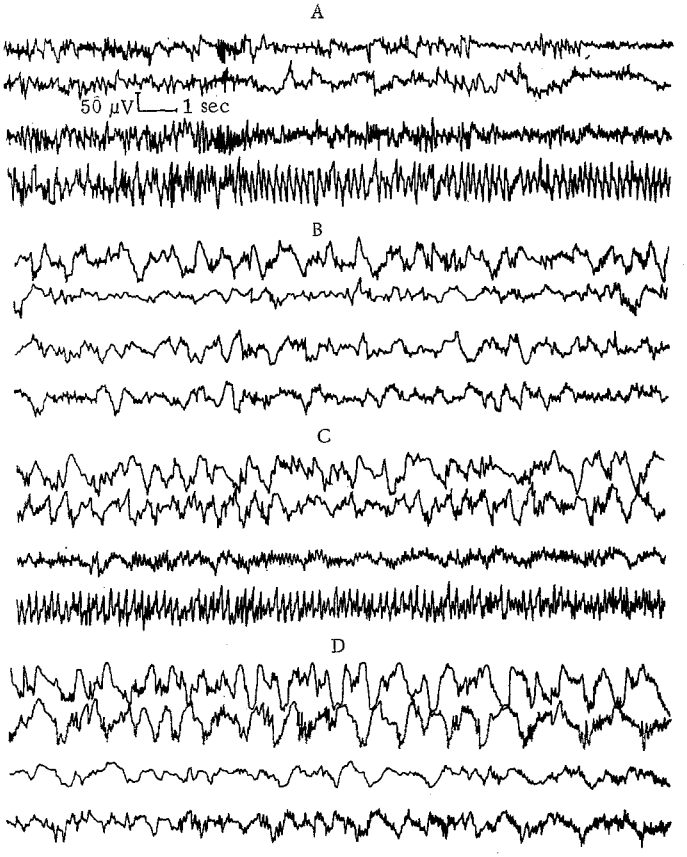

Fig. 2. Effect of oxotremorine on bioelectrical activity of various parts of the rabbit brain after premesencephalic section. From top to bottom: EEG of right sensorimotor cortex, anterior and middle parts of right gyrus cinguli, right dorsal hippocampus, and pontomesencephalic reticular formation. A) EEG of rabbit with intact brain; B) EEG of rabbit 1 h after premesencephalic section and before injection of drugs; C) 5 min after intravenous injection of oxotremorine (0.15 mg/kg); D) 5 min after intravenous injection of benactyzine (0.6 mg/kg).

It is interesting to note that when only the RF was excluded, but the lateral portions of the brain stem were preserved, in response to afferent peripheral stimulation of sensory nerves a θ rhythm could be obtained in the hippocampus in the absence of EEG-activation in the neocortex. After sections carried out more rostrally than premesencephalic, cutting off also the posterior hypothalamus, the anticholinesterase and cholinomimetic drugs did not produce a θ rhythm in the structures of the limbic system.

The hypothesis has been put forward [4, 7, 10] that the appearance of a θ rhythm in the hippocampus is dependent on intact pathways between the RF and the hippocampus. The premesencephalic section experiments, with complete cutting off of the brain-stem RF, showed that the presence of such connections is not essential for the appearance of a θ rhythm in the hippocampus in response to injection of anticholinesterase and cholinomimetic drugs. Probably in the experiments of Torii and Wikler [11], after sections through the mesencephalon, connections with the anterior portions of the mesencephalic RF were not completely destroyed because they observed EEG activation in the cortex also after injection of physostigmine.

Consequently, the results of the present investigation suggest that the appearance of a regular reticular rhythm in the pontomesencephalic RF is independent of the θ rhythm in the hippocampus. At the same time, the regular rhythm in the occipital cortex in rabbits and the reticular rhythm in the pontomesencephalic RF share a common cause because they result from excitation of the ascending reticular activating system.

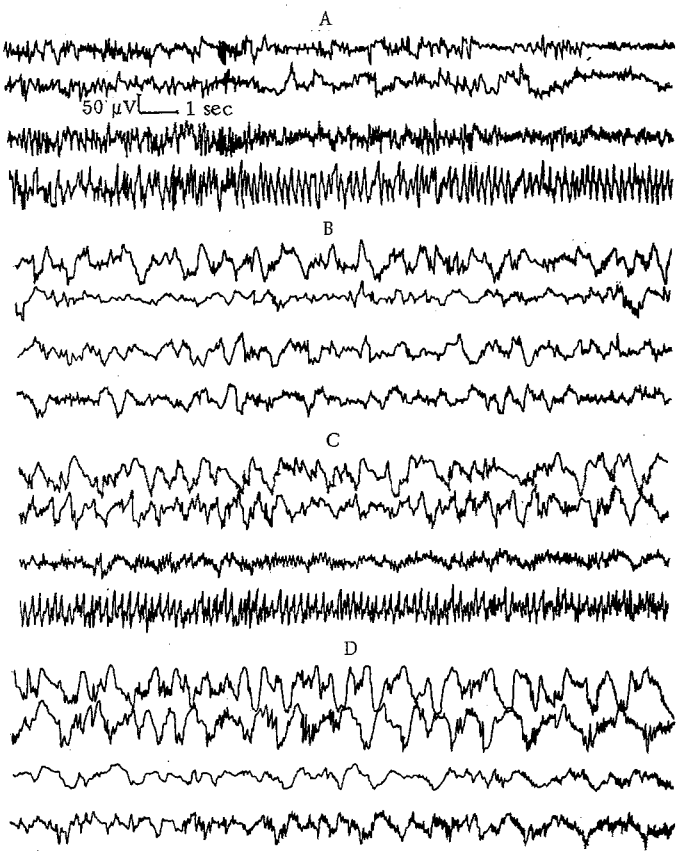

Fig. 3. Effect of galanthamine on bioelectrical activity of the cortex and structures of the limbic system of a rabbit after premesencephalic section. From top to bottom: EEG of right sensorimotor cortex, right visual cortex, septum, right hippocampus. A) EEG of rabbit with intact brain; B) EEG of rabbit 1 h after premesencephalic section and before injection of drugs; C) 5 min after intravenous injection of benzacine (0.6 mg/kg).

It may be postulated that the limbic system possesses its own muscarine-like cholinergic mechanism. The appearance of a θ rhythm in the hippocampus following administration of anticholinesterase and cholinomimetic drugs is the result of a change in activity of this mechanism of the limbic system, in which probably the cholinergic mechanisms of the posterior hypothalamus and septum play an important role. This hypothesis is supported by disappearance of the θ rhythm in the hippocampus after destruction of the septum [6], after injection of procaine [5] and of the M-cholinolytic benactyzine (data obtained in this laboratory by Yu. F. Pastukhov) into the septum, and also by disappearance of the θ rhythm when the posterior hypothalamus was destroyed in animals with premesencephalic section.

Consequently, the cholinergic mechanisms of the limbic system and of the ascending reticular activating system are not components of the same brain system. They are parts of different functional systems of the brain which possess their own neurochemical mechanisms. In the intact brain these two systems are closely interconnected and they may work as a single entity.

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