ANALYSIS OF THE NEUROHUMORAL MECHANISM FOR ACTIVATION OF THE CORTEX BY DIFFERENT KINDS OF STIMULI

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It has long been known that there are cholinergic [14] and adrenergic structures [6, 11, 12, 17, 18] in various parts of the central nervous system, including cortex and subcortical formations. No particular interest, however, was taken in these structures until after discovery of the ascending activating influence of the reticular formation on the cerebral cortex [13] and formulation of the theory that cholinergic [14] and adrenergic [3, 10, 15] mechanisms were concerned in these effects.

It had earlier been suggested that the activating influence of the reticular formation on the cerebral cortex was nonspecific, that it was always the same, irrespective of the kind or biological significance of the stimulation experienced [13]. This idea was based on the fact that, whatever the form of excitation, the active state of the cortex was invariably expressed by the same electroencephalographic changes - a desynchronization reaction.

It has, however, been established by a series of investigations, carried ou in Anokhin's laboratory [1, 8, 9], that different kinds of ascending activating effects, which are determined by the biological properties of the stimulation employed and the associated activity, are represented by the same reaction of desynchronization. This opens the way for the new concept that the activating effect from the reticular formation on the cerebral cortex is always specific in reactions of different biological kind [3].

On the other hand, recent investigations have shown that cerebral cholinergic structures are not all of the same kind, but include both M-cholinergic and N-cholinergic elements [2, 4, 7]. There are more M-cholinergic than N-cholinergic elements in the ascending activating reticular system [2, 4, 16].

In view of these facts it is of primary importance to determine whether the neurohumoral mechanisms of ascending activating effects of different biological quality are the same or different.

An attempt was therefore made to analyze M-cholinergic and N-cholinergic mechanisms in reactions of cortical activation evoked by different kinds of stimuli - nociceptive, acoustic, and produced by injection of acetylcholine and adrenaline.

METHODS

The experiments were carried out on rabbits, lightly anesthetized with urethane (800 mg/kg). Electrical activity was recorded from the sensorimotor, temporal and occipital regions of the cortex on both sides. Potentials were collected by means of needle electrodes, inserted into the cranial bone. Blood pressure (in femoral artery) and EEG were recorded simultaneously. The various indices were recorded by a 17-channel ink-writing oscillograph. Reactions of EEG activation were produced by injection of acetylcholine and adrenaline, continuous electrical stimulation of the sciatic nerve (rectangular pulses: 1 msec, 100 c/s, 5-12 V) and acoustic stimulation. Acetylcholine (0.4-2.0 μg/kg, sometimes 5-10 μg/kg) were injected in the direction of the brain through a fine polyethylene tube inserted into the thyroid artery (towards the common carotid) or the vertebral artery.

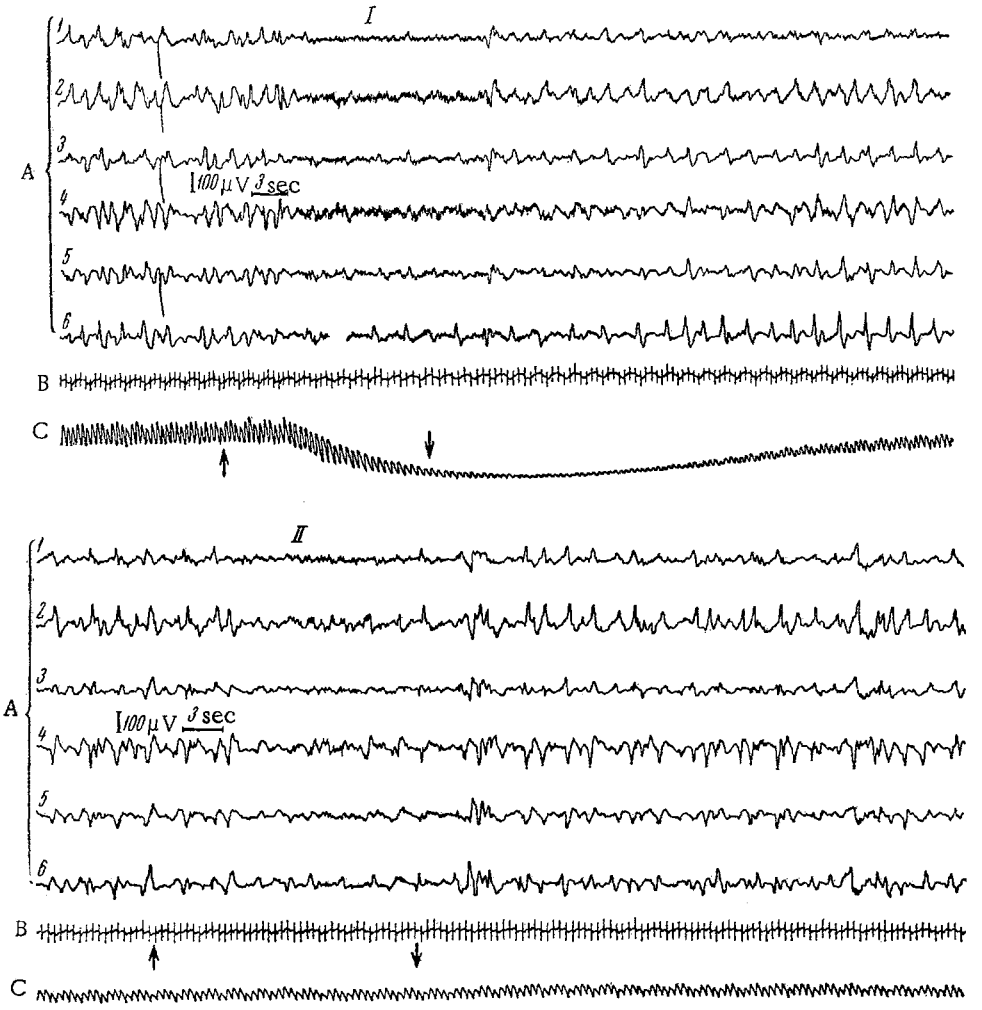

Fig. 1. Effects of injection of acetylcholine (1 μg/kg) into carotid artery before (I) and after (II) injection of atropine (150 μg/kg). A) EEG: unipolar recording from sensorimotor (1-right; 2-left), temporal (3-right; 4-left) and occipital (5-right; 6-left) regions of cortex. B) ECG. C) arterial pressure. Arrows-beginning and end of injection of acetylcholine.

RESULTS

In normal, lightly anesthetized rabbits an injection of acetylcholine towards the brain led to fall of blood pressure and development of a reaction of desynchronization in the EEG (Fig. 1I).

The arterial pressure usually began to fall 8-12 sec after the commencement of the injection . The degree and duration of the fall depended directly on the quantity of acetylcholine injected. The reaction of desynchronization sometimes developed at the same time as the fall in blood pressure, but it might also precede or follow the latter. The duration and intensity of the reaction of desynchronization depended both on quantity of acetylcholine injected and depth of anesthesia. The depressant effect of acetylcholine is known to be connected with mobilization of vascular M-cholinergic receptors, and is abolished by small doses of atropine, whereas the effect of acetylcholine on N-cholinergic systems is only suppressed by larger doses of the cholinolytic.

In attempting to determine what parts M-cholinergic and N-cholinergic structures play in the development of a cholinergic reaction of activation in the cortex, it was assumed that, if the cerebral structures concerned with the production of this reaction were exclusively M-cholinergic, then very small doses of atropine would suffice to prevent the acetylcholine depressor reaction, and would also abolish the reaction of EEG desynchronization. If, on the other hand, these structures had the properties of N-cholinergic systems, small doses of atropine would suppress only the depressor effect of acetylcholine, and not the reaction of desynchronization. Furthermore, if the neurons

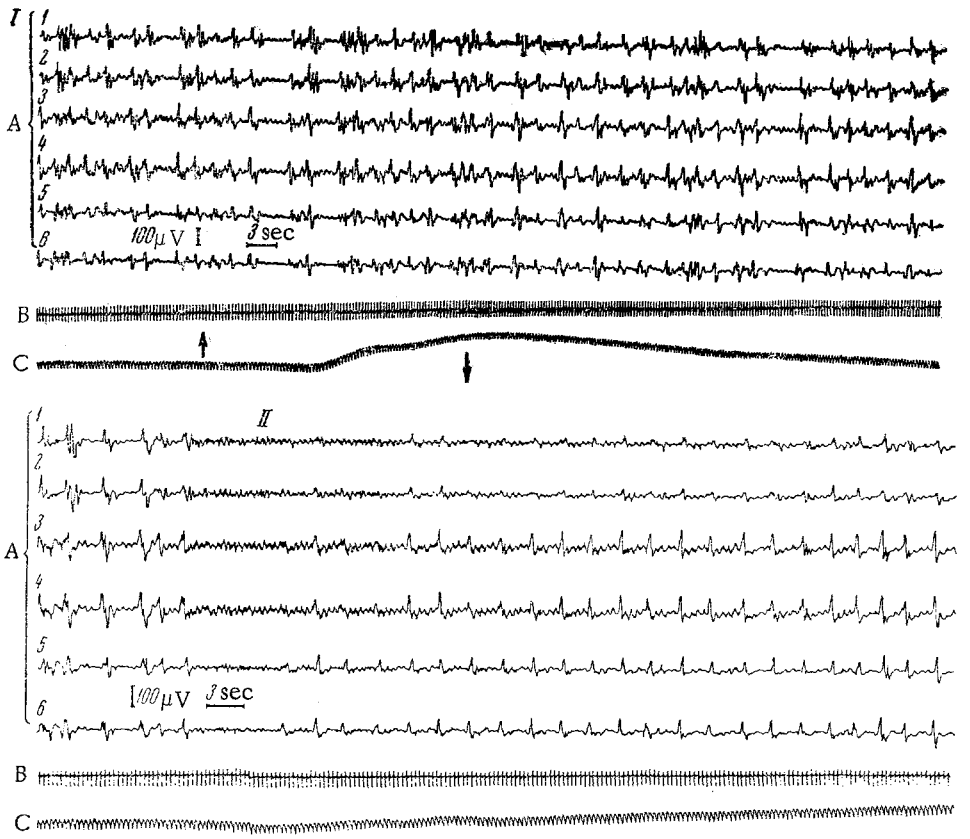

Fig. 2. Effects of intracarotid injection of adrenaline immediately (I) and 3 min (II) after injection of atropine (100 μg/kg). Notation as in Fig. 1.

and synapses concerned in production of the cholinergic reaction of cortical activation are N-cholinergic, large doses of atropine would abolish both the depressor and EEG-desynchronizing effects of acetylcholine.

It was found in these experiments that the injection of acetylcholine 60-90 sec after injection of atropine 150-200 μg/kg produced a less intense reaction of EEG activation, associated with either a very slight fall, a slight rise or no change in blood pressure (Fig. 1II). A preliminary injection of atropine 400-600 μg/kg reduced or abolish both depressor and EEG-desynchronizing effects of acetylcholine, injected in doses of 0.4-2.0 μg/kg. Sometimes in these experiments the acetylcholine produced a transient increase of blood pressure, but this was not accompanied by any EEG changes. But, even when administered 10-13 min after atropine, acetylcholine was already beginning to produce a reaction of EEG desynchronization, but without fall of blood pressure.

The injection of adrenaline into a carotid or vertebral artery was followed at once by increase of blood pressure, often associated with slowing of the heart. With this slowing there was often increase of ECG amplitude. In some cases, small doses of adrenaline produced merely pressor reactions, the ECG remaining unchanged. The pressor reactions were not associated with EEG desynchronization, and, indeed, larger and slower potentials were often recorded (Fig. 2I). A reaction of EEG desynchronization developed when the blood pressure returned to its original level (Fig. 2II). Small doses of atropine, injected 2-3 min before the injection of adrenaline, did not prevent the rise of blood pressure, but they prevented development of EEG desynchronization. When the adrenaline was injected 10-12 min after the injection of atropine, EEG desynchronization developed as the blood pressure was restored to its original level.

The injection of 0.5 ml normal saline towards the brain had no effect on the various indices under examination.

In states of light urethane anesthesia acoustic stimulation produced a local reaction of desynchronization, limited to the temporal and occipital regions of the cortex (Fig. 3I). This reaction was abolished by the injection of small doses of atropine (Fig. 3II). In contrast, nociceptive stimulation of the sciatic nerve produced a generalized

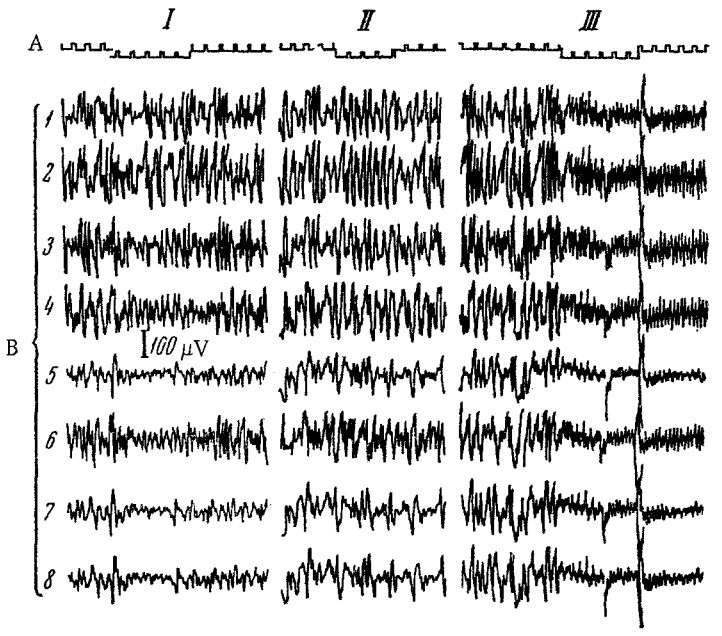

Fig. 3. Effect of acoustic stimulation on EEG before (I) and after (II) injection of atropine (150 μg/kg) and effect of painful stimulation on EEG after injection of atropine into carotid artery (III). Depression of EEG-desynchronizing effect of acoustic stimulation clearly evident. A) Time scale (1 sec). B) EEG: unipolar recording from anterior (1-right; 2-left) and posterior (3-right; 4-left) sensorimotor regions, and from temporal (5-right; 6-left) and occipital (7-right; 8-left) regions of cortex. Drop in time scale indicates period of stimulation.

reaction of desynchronization (Fig. 3III), which was not blocked by atropine in the doses employed in these experiments, but was abolished by chlorpromazine.

When these results are considered in the light of current ideas that the reaction of desynchronization in the EEG observed when acetylcholine is injected intra-arterially towards the brain is connected with excitation of the cholinergic substrate of the ascending activating reticular system, and that the blockade of this reaction produced by injection of atropine is the result of depression of this substrate, it must be assumed that, in the conditions of these experiments, in which the depressor reaction was suppressed, the cortical activation was connected with excitation of N-cholinergic structures. If, in fact, these structures had been exclusively M-cholinergic, they would have been blocked by the injection of small doses of atropine, which abolished the depressor (muscarine-like) effect of acetylcholine. The involvement of N-cholinergic structures in the development of cortical activation, induced by the intra-arterial injection of acetylcholine towards the brain, was also evidenced by the results of some other experiments.

Large doses of atropine, which block both M-cholinergic and N-cholinergic systems, abolished both the depressor and EEG-desynchronizing effects of acetylcholine. In these experiments, however, the period for which the reaction of desynchronization was suppressed was less than the corresponding period for the depressor acetylcholine effect on blood pressure. The only possible explanation for this is that the cholinergic reaction of cerebral activation is produced by cerebral and N-cholinergic receptors.

In the experiments in which M-cholinergic structures were blocked the reaction of desynchronization caused by acoustic stimulation or the injection of adrenaline was abolished. This suggests that the cortical activation produced in these ways were connected with mobilization on M-cholinergic structures. Also, as the pain-induced reaction of desynchronization, which was suppressed by injection of chlorpromazine [1], was not abolished by injection of atropine in the doses used in these experiments, this activation could naturally be considered an adrenergic mechanism.

The latest results from the Anokhin laboratory have shown that activation, recorded in the anterior parts of the cortex in animals fasted for 24 h [8], are not suppressed by chlorpromazine, but are blocked by the intramuscular injection of small doses of atropine or the application of Amizil or atropine directly to the cortex. It follows, therefore, that the reaction of cortical activation, recorded in the fasting animal, can also be connected with the activity of M-cholinergic structures.

The results described thus confirm the concept that ascending reticular effects on the cortex may be of various kinds and may be specific, and that there are different chemical mechanisms in the functional systems "responsible" for the production of these effects.

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