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FORMATION OF COMPLEXES OF EPILEPTIC ACTIVITY IN THE CEREBRAL CORTEX UNDER THE INFLUENCE OF A DETERMINANT FOCUS INDUCED BY ACETYLCHOLINE

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Foci of enhanced excitability, with independent discharge patterns, were created by means of weak solutions of strychnine and penicillin in cats. The creation of a hyperactive focus by means of acetylcholine (ACh) and neostigmine led initially to an increase in the amplitude and frequency of the paroxysmal discharges in the nearest foci of activity, and later in foci remote from the hyperactive focus. Qualitative changes subsequently developed in the pattern of activity of the strychnine and penicillin foci (with the appearance of ACh-activity in them) and a single functional complex of foci with the same discharge pattern as the ACh-focus was formed. The latter thus plays the role of determinant structure. Inhibition of the activity of the determinant focus was followed by disappearance of ACh-activity in the other foci, restoration of original (penicillin or strychnine) activity in them, and destruction of the epileptic complex.

KEY WORDS: determinant focus; epileptic complex; neocortex; strychnine; penicillin; acetylcholine.

Previous investigations showed [3-6] that a focus of powerful excitation created in the orbital or temporal region of the cerebral cortex can play the role of a determinant structure [1,2], i.e., one which determines the character of activity of other separate foci of paroxysmal activity, strengthens excitation in them, unites them into a single functional complex, and determines the behavior of the complex as a whole. Such a complex could be destroyed by inhibiting the action of the determinant focus, whereas disconnection of the other foci forming the complex had no significant effect on its behavior. In the investigations cited above a focus created by means of strychnine and penicillin, which disturbed various types of inhibition [7-11], possessed determinant properties.

In the present investigation acetylcholine (ACh) was used to create the determinant focus.

The use of ACh is interesting from several points of view. It is known to cause direct depolarization of neurons [12,13]; the mechanisms of formation and the functional structure of the focus of activity arising under the influence of ACh differ from those produced by the action of strychnine and penicillin; the character of activity in an ACh-focus is also different in principle. The question arose whether such a focus could play

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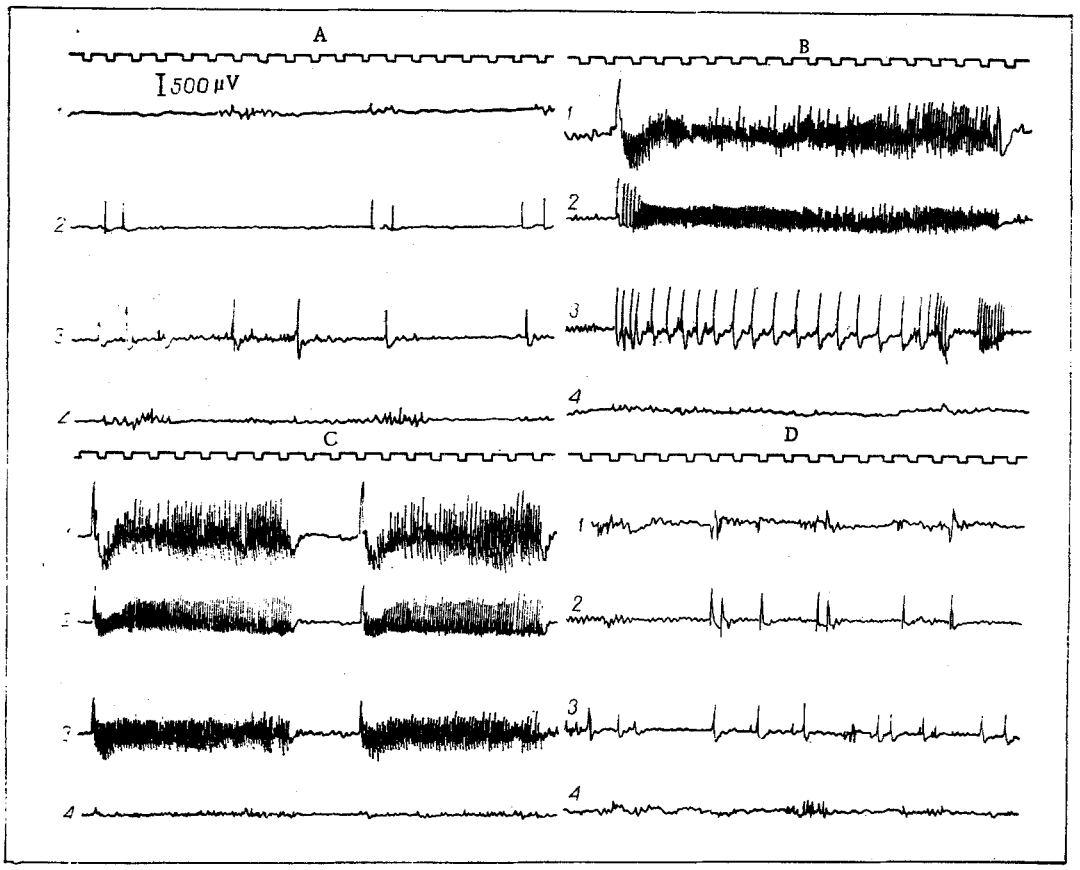

Fig. 1. Effect of determinant ACh-focus on character of activity of foci of epileptic complex. A) Formation of foci of enhanced excitability in zones 2 and 3; 0.5% penicillin applied to zone 2, 0.1% strychnine to zone 3; application of substances stopped after appearance of epileptic activity; B) first stage (1st minute) of formation of determinant structure in zone 1 by application of 0.5% neostigmine and 10% ACh; C) second stage of formation of determinant focus (3 min after application of ACh to zone 1); D) 2 min after application of 6% pentobarbital to zone 1. Here and in Fig. 2: 1) orbital cortex, 2) coronary cortex, 3) posterior sigmoid gyrus, 4) anterior sigmoid gyrus. Calibration, 500 μV; time marker, 1 sec.

the role of a determinant focus. The qualitatively different pattern of activity in an ACh-focus would make its effect as a determinant structure on other foci (strychnine and penicillin) particularly demonstrative.

EXPERIMENTAL METHOD

Acute experiments were carried out on cats. Under pentobarbital anesthesia (30-40 mg/kg, intraperitoneally) the skin and subcutaneous areolar tissue were divided by a midline incision from the nasal bones to the occiput. The eye was drained. Trephining the cranial bones and orbit provided wide access to the various parts of the frontal and parieto-occipital regions of the neocortex of one hemisphere. Separate foci of paroxysmal activity were created by application of filter paper (2 mm^2) soaked in 0.1-0.5% strychnine nitrate or in 0.3-0.8% of the sodium salt of penicillin. Foci of this sort were created in different parts of the coronary, posterior sigmoid, and lateral gyri. A focus of powerful epileptiform activity was created in the orbital cortex by application of 0.5-10% ACh after preliminary treatment of that part of the cortex with 0.1-0.5% neostigmine. The foci were inactivated by local application of 6% pentobarbital. Potentials were recorded by a monopolar technique; the reference electrode was fixed in the nasal bones and the active electrodes consisted of cotton threads soaked in Ringer's solution. The potentials were recorded on a 4-EEG-3 ink-writing electroencephalograph.

EXPERIMENTAL RESULTS

Between 40 and 50 sec after application of 0.5% penicillin solution to the coronary gyrus slow waves appeared at the site of application, 1-3 min later monophasic spike discharges varying in amplitude and

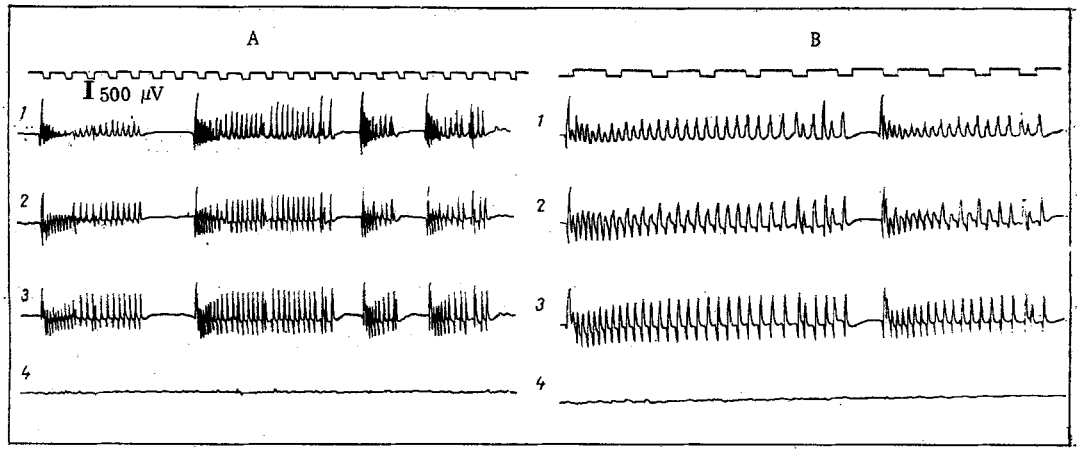

Fig. 2. Changes in pattern of activity of "strychnine" foci of complex under influence of determinant ACh-focus. A) Activity of foci 2 min, B) 3 min after creation of determinant focus in zone 1 by means of 0.5% ACh and 0.5% neostigmine. Foci in zones 2 and 3 created by application of 0.1% strychnine.

frequency were observed, and a few minutes later still these gave way to high-amplitude negative paroxysmal potentials. Simultaneously with the penicillin focus, a strychnine focus of epileptic activity was formed in the posterior sigmoid gyrus, in which monophasic negative discharges of varied amplitude were recorded first, followed by characteristic triphasic potentials. At the stage when the two foci generated asynchronous short (30-40 msec) paroxysmal potentials (Fig. 1A, zones 2 and 3), varying in amplitude and frequency, neostigmine with ACh was applied to the rostral part of the orbital cortex. Between 2 and 4 min after application of neostigmine and ACh, an increase in the amplitude and frequency of the epileptic discharges was observed in the penicillin and strychnine foci. Another few minutes after application of ACh, negative spike potentials appeared in the orbital cortex, followed by characteristic regular epileptic discharges consisting of a high-amplitude positive-negative spike and after-discharge (Fig. 1D, zone 1). In the course of formation of the ACh-focus and the increase in the level of its activity a sharp increase in the number of paroxysmal discharges was observed in the focus in the coronary gyrus, synchronous with the rhythm of the after-discharges of the ACh-focus (Fig. 1B, zone 2). During this period epileptic discharges characteristic of the penicillin focus (the initial part of the discharge), were still recorded in this zone, together with rhythmic low-amplitude discharges synchronized with those of the ACh-focus. In a zone of the posterior sigmoid gyrus more distant from the orbital cortex triphasic strychnine discharges continued to be recorded, although their number was sharply increased, and grouped discharges appeared at certain periods (Fig. 1B, zone 3). In the anterior sigmoid gyrus, which was not treated with any convulsants, at this time and later as a rule no epileptic discharges were present, or only single discharges of low amplitude were recorded.

Regular epileptic discharges synchronized with discharges of the ACh-focus in the orbital cortex also were generated in the posterior sigmoid gyrus (zone 3) 3-10 min after creation of the ACh-focus. At this stage both the strychnine and the penicillin foci generated activity characteristic of the ACh-focus (Fig. 1C). A single functional complex consisting of three foci of epileptic activity, with a discharge pattern imposed by the ACh hyperactive focus in the orbital cortex, thus appeared. It is important that the ACh-focus modified the character of activity of the penicillin and strychnine foci not only quantitatively, but also qualitatively to a significant degree. These changes are clearly visible also in Fig. 2, which shows the results of an experiment in which foci were created in zones 2 and 3 by means of 0.1% strychnine and a focus in zone 1 by application of 0.5% neostigmine and 0.5% ACh. In the functional complex thus formed the foci in zones 2 and 3 constituted a heterogeneous functional formation: Immediately after a hypersynchronized biphasic spike, characteristic of ACh-focus (zone 1) paroxysmal potentials followed, with a positive deflection characteristic of strychnine spikes; the amplitude of the positive wave then diminished gradually and it could become ill defined (as in the ACh-focus) and the amplitude of the negative waves increased. This pattern of activity was more marked in the focus closer to ACh (zone 2) and less marked in the distant focus (zone 3). Biphasic epileptic discharges with a marked negative wave, characteristic of strychnine foci, were recorded in the latter. Meanwhile the second positive wave, following the negative wave and also characteristic of the typical strychnine discharge, was absent in this focus as in the rest. The discharge frequency in foci 2 and 3 was the same as in the ACh-focus.

As the data given above show, under the influence of the determinant ACh-focus something resembling hybridization of activity took place in the other foci of the complex, in which activity characteristic of the ACh-focus and of the other foci was reflected. This "hybridization" was particularly characteristic of the transition stage in the development of the complex. This was followed by the appearance of complete imposition of ACh-activity on all foci of the complex. Sometimes, however, this "hybrid" activity could persist as the apparent end result.

After establishment of a stable rhythm of synchronized activity in all the foci the filter paper with ACh was removed from the orbital cortex and the foci continued to generate synchronized discharges. Later a decrease was observed in the amplitude, frequency, and duration of the epileptiform discharges in all the foci, the strychnine and penicillin discharges were restored in the foci, and they then disappeared.

To make sure that it was in fact the ACh-focus in zone 1 that was the determinant structure responsible for the character of activity on the other foci of the complex, experiments with pharmacological inhibition of activity of each of the foci were carried out. After application of pentobarbital solution to the region of the hyperactive focus in the orbital cortex (at the stage when all foci of the complex had the same synchronized discharge pattern) epileptiform activity in this focus diminished sharply after a few minutes. The acetylcholine character of activity in the other foci (zones 2 and 3) disappeared and epileptic discharges typical of penicillin and strychnine appeared. Each of the foci generated asynchronous, independent discharges (Fig. 1D), i.e., the complex disintegrated and the residual foci in zones 2 and 3 became autonomous, as they had been before the formation of the complex under the influence of the determinant focus (Fig. 1A). Application of pentobarbital to the other foci in the coronary or posterior sigmoid gyrus led to inhibition of activity only in that same focus; the remaining foci continued to give synchronized discharges as before.

The investigations thus showed that a focus of hyperactivity induced by means of ACh can play the role of a determinant focus. These results, together with those of previous investigations [1-6], are evidence that the factor responsible for the determinant properties of the focus is the power of the functional volley which they generate. The functional volley from the determinant focus does not simply intensify the activity of the dependent foci, but it can also induce complex qualitative changes in the character of their activity. Under the influence of impulses from the determinant focus, the intrinsic activity of the dependent foci may be suppressed and then transformed to correspond to the character of epileptic activity of the determinant focus.

These experiments also showed the complex character of relations between the determinants and dependent foci. These relations were determined primarily by the level of activity of the determinants and dependent foci. On the creation of separate foci by application of strychnine solutions of different concentrations the ACh-focus imposed the character of its own activity primarily on foci with epileptic potentials of low amplitude, whereas the other foci continued to generate typical strychnine discharges. The relations between the foci also depended on the distance between the determinants and other foci. The more distant foci did not conform to the character of activity of the ACh-focus until much later (Fig. 1B, zone 3), and sometimes not at all. Nevertheless, the dependent foci are not passive structures which simply submit to the influence of the determinant factors. In some experiments, in the initial stages of formation of the ACh-focus, when the excitability of this part of the cortex had just started to increase and the level of its activity was lower than in the strychnine foci, it was noted that the latter could induce potentiation of paroxysmal activity in the ACh-focus. Sometimes, evidently in those cases when the relative strengths of activity of the foci remained the same, this potentiation of activity in the ACh-focus remained and its discharges conformed to the features of activity of strychnine or penicillin foci. In most experiments, however, as the amplitude and frequency of the potentials in the ACh-focus increased, the latter imposed the character of its own activity on the strychnine and penicillin foci, which became dependent foci. On the whole, the investigations confirm, with a new model, the role of determinant structures in the activity of the nervous system.

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EFFECT OF HYPERBARIC HYPEROXIA ON HUMAN PLASMA ERYTHROPOIESIS INHIBITORS

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In persons unadapted to hyperbaric hyperoxia, 24 h after exposure in a pressure chamber to an increased pressure corresponding to a depth of 63 m (with 25% O_2 in the inspired air), erythropoietins completely disappeared from the plasma, but erythropoiesis inhibitors appeared instead.

KEY WORDS: hyperbaric hyperoxia; erythropoiesis inhibitor; erythropoietin; erythropoiesis.

Few investigations have been undertaken of the action of hyperbaric hyperoxia on erythropoietic activity of the blood in various species of animals [3,10,13]. The answer to the question of how hyperbaric hyperoxia affects the erythropoietic properties of human plasma is not only of theoretical, but also of great practical importance, for nowadays man frequently has to stay and work under conditions of increased partial oxygen pressure both under water and elsewhere.

The object of this investigation was to study the erythropoietic properties of the plasma and composition of the peripheral red blood in persons exposed for the first time to the action of hyperbaric hyperoxia.

EXPERIMENTAL METHOD

Tests were carried out on ten healthy male students aged 18-19 years before and 24 h after a stay in a continous-flow decompression chamber under a pressure of 7.3 kgf/cm^2, equivalent to a depth of 63 m. During their stay at this "depth" the subjects breathed (by means of a special breathing apparatus) an atmosphere consisting of 25% oxygen, 15% helium, and 60% nitrogen. The pressure in the chamber was raised from 1 to 7.3 kgf/cm^2 in the course of 5 min (the partial oxygen pressure – pO_2 – rose to 1.83 kgf/cm^2, i.e., about 1400 mm Hg). The subjects remained under these conditions for 10 min. Pressure in the chamber was then lowered to 2.6 kgf/cm^2 and the subjects started to breathe almost pure oxygen – 98% O_2 (pO_2 2.5 kgf/cm^2), while decompression continued. The whole "lifting" of the subjects from a "depth" of 63 m to sea level occupied about 40 min. None of the subjects had ever previously been exposed to either hyperbaric conditions or hyperoxia.

The erythropoietic activity of the plasma and the hemoglobin concentration, erythrocyte count, and hematocrit index of the peripheral blood were determined before and 24 h after the beginning of the experiment. Erythropoietic factor was determined by studying the mitotic activity of a bone marrow culture in liquid medium in the presence of colchicine [8,11] (from the difference between the stathmokinetic indices of the erythroblasts after addition of the test plasma and of Hanks' solution to the culture) and expressed in conventional units.

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