ROLE OF HYPERACTIVE DETERMINANT STRUCTURES IN THE CREATION OF FUNCTIONAL COMPLEXES OF SEIZURE ACTIVITY IN THE CEREBRAL CORTEX

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Foci of enhanced excitability, with independent discharge patterns, were created by subconvulsive strychninization in experiments on cats. A focus of more powerful excitation created with the same strychnine played the role of determinant despatch station (DDS). Its importance is that it determines the character of activity of the other foci of excitation, strengthens excitation in them, combines them into a single functional complex, and determines the character of activity of the whole complex. This complex can be destroyed by suppressing the DDS with pentobarbital. Blocking individual destination stations included in the complex does not lead to its destruction.

KEY WORDS: determinant despatch station; destination station; orbital cortex; strychnine; epileptogenic focus; determinant.

Determinant despatch stations (DDS) or determinants are structures of the central nervous system (CNS) which form a functional volley, determine the character of activity of parts of the CNS to which this volley is despatched, and so determine the behavior of the whole system. Hyperactive DDS, arising under pathological conditions when inhibitory mechanisms are disturbed, form a pathologically enhanced functional volley; when created in different parts of the CNS they disturb the activity of the corresponding physiological system, endow them with a pathological character, make them hyperactive, and so evoke the appearance of corresponding neuropathological syndromes [1-5].

It was accordingly interesting to study the relationship between a hyperactive DDS and foci of enhanced functional activity in the cortex, simulating situations characteristic of multifocal epilepsy. It might be expected that a focus of powerful excitation arising following the disturbance of inhibitory processes and a lowering of the threshold of excitability of neurons would play the role of a DDS with respect to other foci of enhanced activity. Such a focus was created by application of strychnine, one of the most adequate models of the epileptogenic focus [11].

EXPERIMENTAL METHOD

Acute experiments were performed on 46 cats. Under pentobarbital anesthesia (25-35 mg/kg, intraperitoneally) the skin and subcutaneous cellular tissue were divided by a midline incision running from the nasal bone to the occiput. The eyeball was drained. Trephining the bones of the cranial vault and orbit gave wide access to the various parts of the frontal cortex. Weak strychninization of areas of the cortex was produced by application of filter paper (2 × 2 mm) soaked in a 0.01-0.05% solution of strychnine nitrate and squeezed dry. As soon as the first seizure potentials appeared, the paper with the strychnine was removed. A focus of powerful activity was created by application of a 3% solution or crystal of strychnine to the orbital zone of the orbitofrontal cortex. This cortical zone was chosen because of the presence of well-defined

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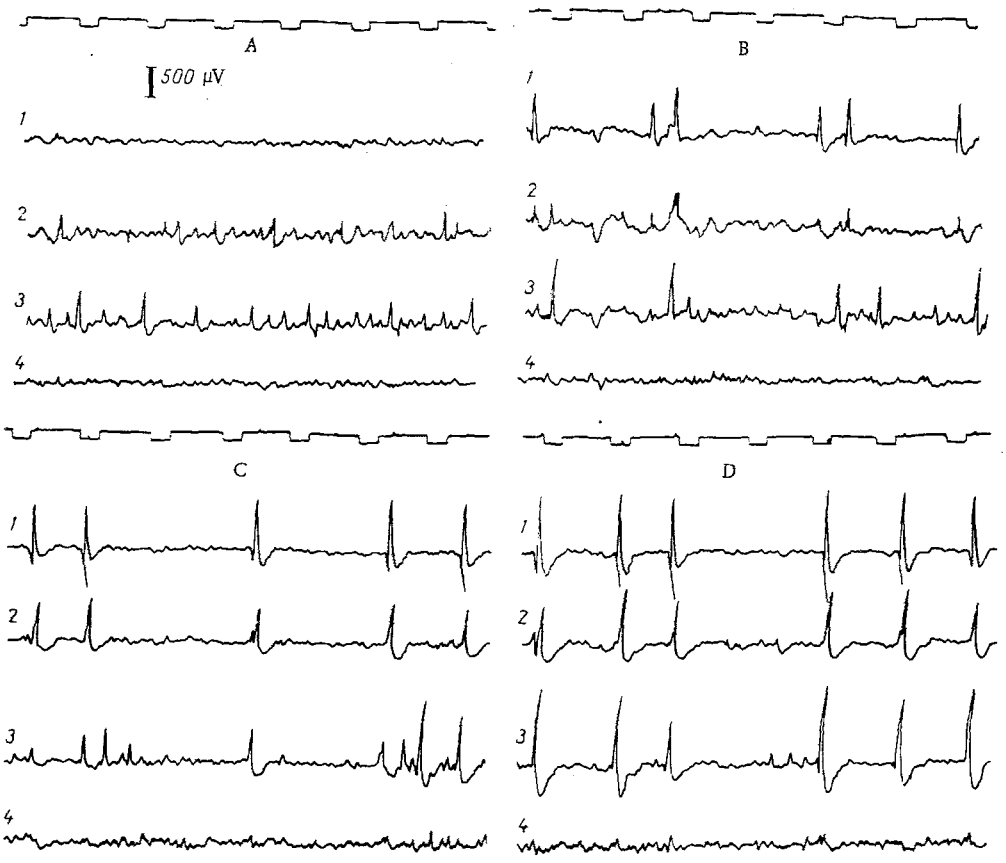

Fig. 1. Synchronization of seizure activity in disconnected foci of excitation in cat cerebral cortex under the influence of DDS (determinants): A) formation of foci of increased excitability in areas 2 and 3 by subconvulsive strychninization (0.01% solution); B) application of strychnine to areas 2 and 3 stopped (paper soaked in strychnine removed), strychnine crystal applied to area 1; initial stage of DDS formation; activity in areas 2 and 3 not yet subordinated to activity in 1; C, D) later stages of DDS formation in 1; activity in foci 2 and 3 increased under the influence of DDS and is synchronized with activity in 1. Calibration: 500 μV; time marker 1 sec; 1) orbital, 2) coronary cortex, 3) posterior, 4) anterior sigmoid gyrus.

afferent-efferent connections with other parts of the neocortex [7, 9, 10] and also the role played by the prefrontal cortex in the generalization of epileptic activity [9]. Pharmacological depression of the foci of activity was achieved by local application of filter paper (2 × 2 mm) soaked in 6% solution of pentobarbital. Biopotentials in the areas of strychninization (orbital, coronary, anterior and posterior sigmoid gyri) were derived by monopolar and bipolar methods and recorded on the 4-ÉÉG-3 ink-writing electroencephalograph.

EXPERIMENTAL RESULTS

Application of strychnine in a weak concentration (0.01-0.05% solution) to the coronary and posterior sigmoid gyri led to the appearance of strychnine potentials of different magnitude, not exceeding 400 μV in amplitude (Fig. 1A). The strychnine spikes in these foci were unsynchronized. Application of the 3% solution or crystal of strychnine to the orbital cortex under these conditions led to the appearance of characteristic triphasic strychnine potentials, with an amplitude of 1.5-2.0 mV, at the site of strychninization. Initially the discharges in all stimulated parts of the cortex arose asynchronously and independently of each other. Later, with enhancement of the strychnine potentials in the orbital cortex, a gradual increase in spike amplitude was observed in the coronary and sigmoid gyri (Fig. 1B, C). This was followed by synchronization of the rhythms of spike activity of the hyperactive focus in the orbital cortex and the other foci; synchronous discharges appeared first in the coronary gyrus, in a situation closer to the orbital cortex; at this time discharges in the posterior sigmoid gyrus still continued to be generated asynchronously (Fig. 1B). Synchronization of spike activity in the orbital cortex and in the posterior sigmoid gyrus, more remote from it than the coronary cortex,

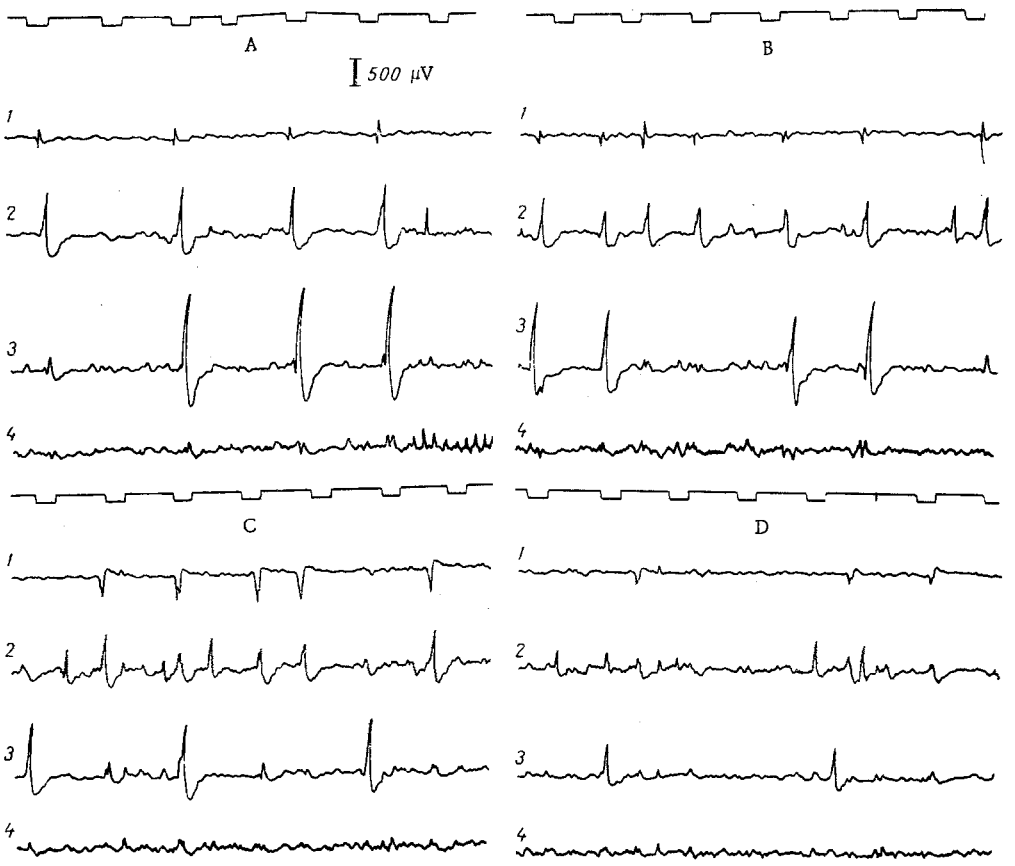

Fig. 2. Behavior of DDS–DS complex on application of 6% pentobarbital solution to region of DDS: A) 15 sec, B) 10 min, C) 15 min, D) 20 min after application of 6% pentobarbital solution. Remainder of legend as in Fig. 1.

appeared later. At the height of development of the process (Fig. 1D) all foci of excitation were firing synchronously, with the same pattern, determined by the firing pattern of the hyperactive focus in the orbital cortex. Besides synchronization of activity there was also an increase in amplitude of the spike potentials in the coronary and posterior sigmoid gyri (Fig. 1D). Meanwhile, in the anterior sigmoid gyrus, which was not subjected to preliminary strychninization, no spike activity developed and only isolated potentials of low amplitude appeared sporadically in it (Fig. 1C, D).

Removal of strychnine from the area in the orbital cortex and subsequent rinsing of this area with physiological saline led to a gradual decrease in the discharges not only in the orbital gyrus, but also in the coronary and posterior sigmoid gyri. Soon after, discharges in the latter began to arise asynchronously with the discharges in the orbital cortex; the focus farthest from the orbital cortex in the posterior sigmoid gyrus acquired this "independence" sooner, followed by the focus in the coronary cortex. If, after removal of the strychnine from the orbital cortex and the development of asynchronous activity of the other foci, strychnine was reapplied to the orbital cortex, a gradual increase in amplitude of the discharges was observed in the dependent foci, activity of which was subordinated to that of the hyperactive focus in the orbital cortex.

To discover whether the hyperactive focus does in fact play a determinant role in shaping the character of activity of the other foci, experiments were carried out in which each of those foci was blocked pharmacologically. After application of filter paper soaked in a 6% solution of pentobarbital to the region of a hyperactive focus in the orbital cortex (after rinsing to remove strychnine in the stage when all foci were working according to the same synchronized pattern), the activity in that focus diminished sharply in the course of 10-30 sec (Fig. 2A). During that period, high-amplitude synchronized discharges continued to be recorded in the other two foci (Fig. 2A). Later, 10-15 min after the application of pentobarbital to the orbital cortex, the amplitude of discharges in the coronary and posterior sigmoid gyri was reduced and each of them began to fire autonomously and independently of the other (Fig. 2B, C). After the complete suppression of activity in the hyperactive focus in the orbital cortex, complete desynchronization of activity was observed in the other foci (Fig. 2D). Application of pentobarbital to the other foci (coronary or posterior sigmoid gyri) led to

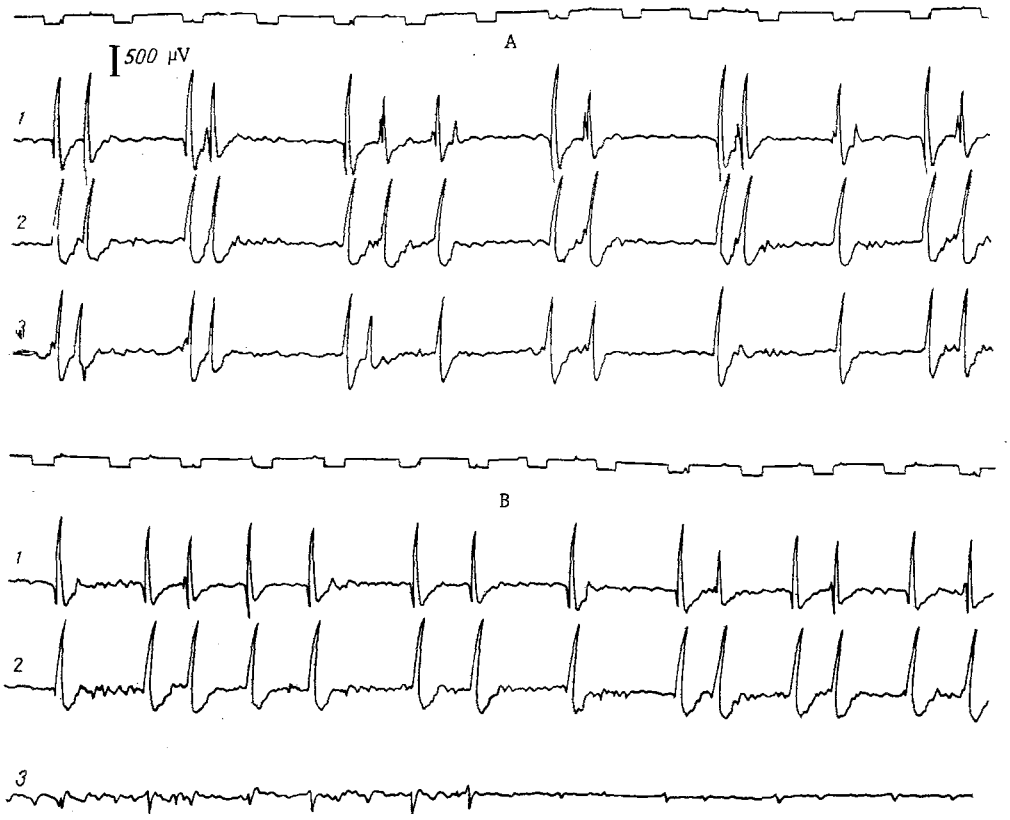

Fig. 3. Effect of inhibition of focus of excitation playing the role of DS on activity of DDS and other DS: A) 20 min after beginning of formation of DDS in area 1; synchronization of spike activity in areas 2 and 3 with activity in 1; B) 2 min after application of 6% pentobarbital solution to DS in area 3. Remainder of legend as in Fig. 1.

inhibition of activity in that same focus only and the other foci continued to fire in accordance with the previous synchronized pattern (Fig. 3).

These experiments thus confirmed the initial hypothesis that a hyperactive focus in the cerebral cortex can play the role of a DDS. The importance of this fact is that it determines the character of activity of other foci of excitation, enhances the excitation in them, unites them into a single functional complex, and determines the character of activity of the complex as a whole. Such a complex is thus converted into what amounts to a single epileptic focus, in which the leading role is played by the DDS (determinant).

The behavior of the independent foci which act as "destination stations" (DS) for the functional volleys formed by the DDS deserves attention. It is evident that the DS do not behave as passive structures, simply reproducing the functional volley from DDS and obeying it. In cases when the DS preserve their own autonomous control systems, the functional volley from DDS can be damped and suppressed in DS. This is clear from the example of behavior of the structures in the anterior sigmoid gyrus, not receiving preliminary strychninization, where induced spike activity was virtually absent or of negligible intensity. Only after the creation of very powerful foci of excitation did induced paroxysmal activity arise in intact areas of the cortex also. The functional volley from DDS was effective in DS, where the thresholds of excitability of the neurons were lowered and inhibitory mechanisms disturbed, as a result of preliminary treatment of these areas of the cortex with a weak solution of strychnine. On the other hand, in some experiments it was observed that the greater the initial activity in DS (the higher the amplitude of its spikes), the stronger the DDS activity had to be in order to be able to "impose" the character of its own activity on DS, and the longer the time required for this effect to be achieved. So that the DDS could exert its effect sufficiently completely, the relations between the intensity of the volley from DDS and the state of preparedness of DS is thus essential, and a very important role in this situation is played by mechanisms of autoregulation and, in particular, inhibitory mechanisms in DS and the level of excitability of their neurons. The example of the disintegration of the functional

complex after blocking of the hyperactive DDS, when the DS become "autonomous" generators, also reveals their role as functionally independent structures.

These investigations show that not every focus of excitation acquires the function of a DDS; only a structure which forms a functional volley of sufficient intensity can do so. Results of the investigation reveal evident differences between the DDS and the dominant focus: Unlike the DDS, the dominant does not potentiate excitation in other foci and does not determine their behavior, but depresses their activity [6]. Coordinated inhibition of activity of other centers and of other reactions is an essential feature of the dominant both as a focus of excitation and as a principle of nervous activity. When defining the leading focus in epilepsy it is thus desirable and more correct to speak of a "determinant focus" and not of a "dominant focus." The investigations described above may help to shed light on the pathogenic structure of many forms of CNS pathology and, in particular, of epilepsy.

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BRAIN ELECTRICAL ACTIVITY OF RABBITS WITH EXPERIMENTAL HERPETIC ENCEPHALITIS

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A clinical and electrophysiological investigation on 33 rabbits with experimental herpetic encephalitis revealed changes in brain electrical activity correlating with the clinical picture of the disease. In the acute period of encephalitis diffuse slowing of the brain potentials was accompanied by paroxysmal activity of two types: paroxysmal periodic complexes and "spike + slow wave" complexes at the rate of three per second.

KEY WORDS: herpes; experimental infection; brain potentials.

Valuable data characterizing the dynamics of the pathological process in the CNS can be obtained by the use of experimental models of herpetic encephalitis. Work so far published deals mainly with the investigation of clinical and morphological changes in animals with herpetic encephalitis [2, 9] and there are only isolated references to the study of brain electrical activity [6].

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