COMPLEXES OF EPILEPTIC ACTIVITY FORMED BY A DETERMINANT FOCUS IN THE CORTEX ISOLÉ

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Foci of increased excitability, functioning independently, were created in the neuronally isolated cortex of cats by means of weak strychnine solutions. The creation of a hyperactive focus by application of concentrated solutions or crystals of strychnine led to an increase of amplitude and discharge frequency in other foci, synchronization of the discharges in these foci, and their combination into a single functional complex of foci driven by the hyperactive focus. The latter thus played the role of determinant structure. Marked generalization of paroxysmal activity also took place under the influence of the determinant focus and was manifested as the spread of epileptic discharges to areas of cortex untreated with strychnine. The results indicate that relations established between hyperactive foci in the cortex and the effects of the determinant structure can be brought about through purely cortical mechanisms.

KEY WORDS: determinant structure; epileptic focus; epileptic complex; strychnine; cortex isolé.

Previous investigations [2-6] have shown that a focus of powerful excitation created in the cortex by means of strychnine can play the role of a determinant structure [1], which determines the character of activity of other scattered foci of epileptic activity, enhances excitation in them, unites them into a single functional complex, and determines the behavior of the complex as a whole. Such a complex of foci can be destroyed by suppressing the activity of the determinant focus; blocking of the other foci included in the complex has no significant effect on the behavior of the complex itself. In the investigations cited above complexes of epileptic activity were created in different parts of the intact neocortex. The next step was to study the role of subcortical structures and cortical structures proper in the mechanism of the relations between these foci. The aim of the present investigation was to study functional relations between foci with different levels of paroxysmal activity created in the cerebral cortex isolated from subjacent structures.

EXPERIMENTAL METHOD

Ten cats were used. The cortex was isolated by Khananashvili's method [7] as follows. Under pentobarbital anesthesia (30-40 mg/kg, intraperitoneally) a piece of bone (20-10 mm) above the anterior part of the lateral gyrus was removed by means of a saw. After the dura had been opened a longitudinal incision was made in the cortex of this gyrus in the anteroposterior direction 10-15 mm long, and was carried down as far as the lateral ventricle. The latter was opened to reveal Ammon's horn, covering the cortical projection pathways (corona radiata) in the region of their maximal concentration. By an incision running in the anteroposterior direction along the lateral surface of the caudate nucleus and lateral border of Ammon's horn, all pathways connecting the neocortex with the basal structures and pathways running in the opposite direction were divided. The operation was performed on one hemisphere, so that it was possible to isolate the cortex of the other hemisphere while keeping the projection pathways intact for control experiments.

Immediately after this operation (acute isolation) or after an interval of 3-10 days (chronic isolation) experiments were carried out to study interaction between foci of epileptic activity in the cerebral cortex. For this purpose the skull was trephined under ether or pentobarbital anesthesia. Foci of paroxysmal activity

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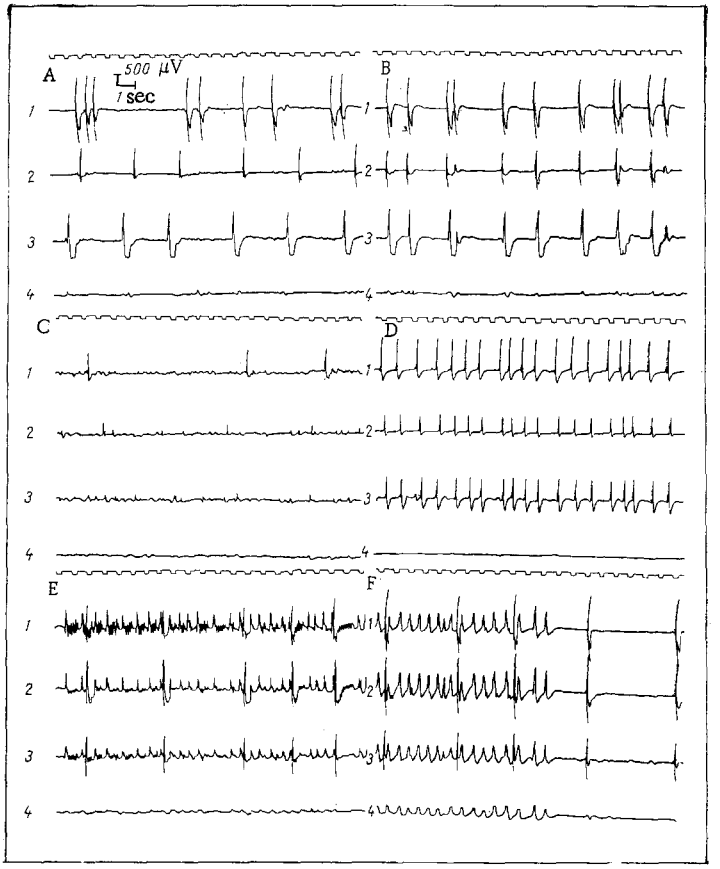

Fig. 1. Formation of an epileptic complex under the influence of a determinant focus in the cortex isolé. A) 1 min after application of strychnine crystal to area 1. Independent foci of paroxysmal activity were created beforehand in areas 2 and 3 by application of 0.1% strychnine solution; after the appearance of strychnine discharges the application of strychnine was stopped. B) 10 min after A; synchronization of discharges in all foci and formation of a complex of epileptic activity; strychnine removed from area 1 and rinsed off with physiological saline; C) 35 min after B; D) repeated formation of determinant focus in area 1 by application of strychnine crystal and repeated formation of complex (enhancement and synchronization of epileptic activity in all foci). E) 14 min after D; further evolution of complex with formation of activity resembling acetylcholine discharges; F) 70 sec after E. Experiment carried out 3 days after isolation of cortex. 1) Orbital cortex; 2) coronary cortex; 3) anterior ectosylvian gyrus; 4) anterior sigmoid gyrus. Calibration, 500 μV, time marker 1 sec.

were created by application of a piece of filter paper (2 mm^2) soaked in 0.1-0.5% strychnine solution in different parts of the coronary, ectosylvian, anterior and posterior sigmoid, and orbital gyri. A focus of powerful paroxysmal activity was created by application of 1-3% strychnine solution or a strychnine crystal to the orbital or coronary gyrus. The foci were blocked by local application of 6% pentobarbital solution. Potentials were recorded by a monopolar technique and the reference electrode was secured in the nasal bones. The completeness of the sections was verified histologically.

EXPERIMENTAL RESULTS

Paroxysmal discharges appeared 2-3 min after application of 0.1% strychnine solution to the coronary (area 2) and ectosylvian (area 3) gyri of one hemisphere (3 days after isolation of the neocortex) in area 2 only. Discharges did not appear in area 3 until 5-6 min after application of strychnine. After the formation of the scattered foci the filter paper with strychnine was removed and an application of a 3% solution or crystal of strychnine was made to the orbital cortex (area 1). In the first stages of formation of the new focus unsynchronized discharges began to appear in all foci independently of one another (Fig. 1A). Later (10-15 min after application of the 3% solution or crystal of strychnine to area 1) synchronization of the discharges was observed in all foci with the discharges in the new focus (Fig. 1B). After the formation of the epileptic complex,

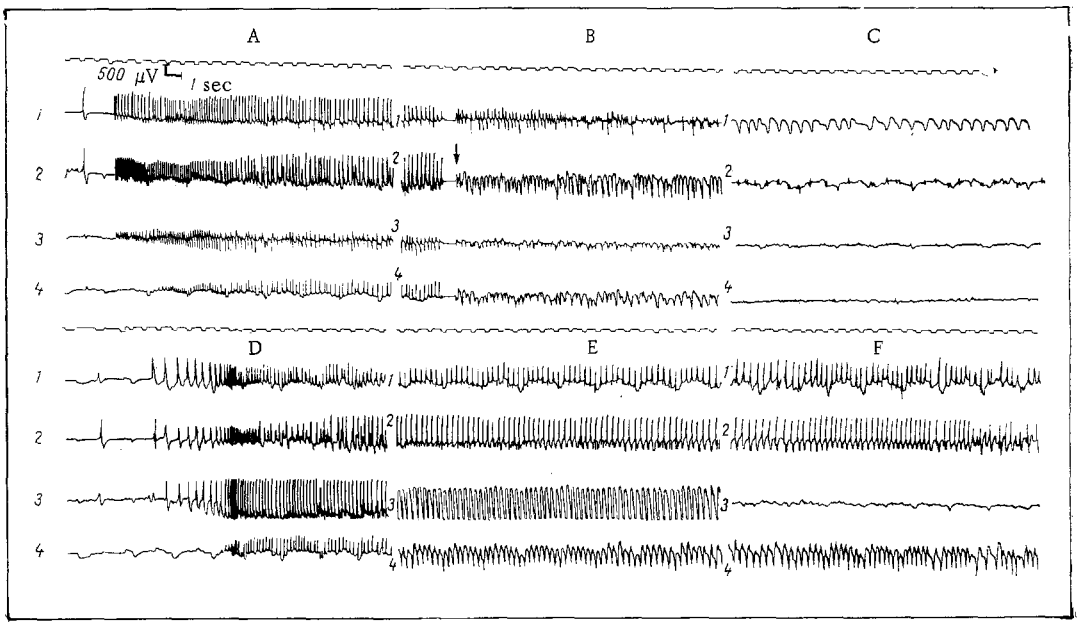

Fig. 2. Role of determinant focus in organization of epileptic complex and onset of generalization of epileptic activity in cortex isolé. A) Focus of paroxysmal activity created in area 1 by application of 0.1% strychnine solution; application of strychnine stopped after appearance of spike discharges. Determinant focus created in area 2 by 1% strychnine solution. Generalization of activity occurred 1 min after formation of determinant focus, involving areas 3 and 4; B) 3 min after A; arrow indicates beginning of effect of application of 6% pentobarbital solution to region of determinant focus; C) 4 min after application of pentobarbital to area 1, destruction of complex; D) re-creation of complex: 0.2% strychnine solution applied to areas 1 and 3, strychnine crystal to area 2; E) 5 sec, and F) 1 min after application of 6% pentobarbital solution to dependent focus in area 3. 1) Coronary cortex; 2) orbital cortex; 3) anterior and 4) posterior sigmoid gyri. Calibration: 500 μV, time marker 1 sec.

strychnine was removed from the region of the hyperactive focus and the region itself was rinsed with physiological saline. A decrease in amplitude of the discharges in the dependent and determinant foci took place 20-30 min after removal of the strychnine. At that period synchronous discharges were still recorded in all foci; a further decrease in the amplitude and frequency of the discharges in all foci and distrubance of synchronization of the discharges were observed 30-40 min after removal of the strychnine (Fig. 1C). If the crystal of strychnine was again applied at this stage to the orbital cortex (area 1) the amplitude and frequency of the discharges in areas 2 and 3 increased again and they became synchronized with discharges in the orbital cortex (Fig. 1D). A new complex of epileptic activity was thus formed and its discharge pattern was determined by the newly activated determinant focus. If the application of strychnine was repeated (and the strychnine not removed) the further evolution of the complex and determinant focus could be observed: Activity recorded during this period differed from typical strychnine spikes and resembled in its electrical characteristics paroxysmal discharges of the spike–after-discharge type (Fig. 1E). These potentials are characteristic of the effect of acetylcholine [6, 8-10]. Meanwhile, besides the discharges mentioned above, paroxysmal potentials typical of strychnine also appeared. A few minutes after the onset of this activity the number of paroxysmal discharges decreased in all foci and the complex continued to generate paroxysmal discharges characteristic of strychnine (Fig. 1F).

In other experiments a focus of relatively weak excitation was created (0.1% strychnine solution) in area 1 (coronary cortex). After it had appeared, a more powerful focus (1% strychnine solution) was formed in area 2 (orbital cortex). The creation of this focus led to the formation of an epileptic complex consisting of two foci, and generating synchronous discharges. In areas not subjected to preliminary strychninization, paroxysmal discharges were absent in the initial period (Fig. 2A, initial fragment). This was followed by a sudden increase in the discharge frequency in both foci up to 5-10 Hz; in the hypoactive focus in area 2, epileptic discharges with a higher frequency than in the dependent focus (area 1) were recorded initially. In regions of the cortex not treated with strychnine (areas 3 and 4) paroxysmal discharges synchronized with those in area 2 appeared in this period, reflecting generalization of paroxysmal activity from the focus in area 2. Discharges of this type appeared first in area 3 (which was nearer), and later in area 4 (more remote from the determinant focus

in area 2). These generalized bursts of paroxysmal activity could last between 1-2 and 6 min, and then they suddenly ceased, so that only single epileptic discharges remained or the original background activity was restored.

Whereas at the generalized discharge stage activity of the determinant focus was suppressed by pentobarbital, after a few seconds the discharges in it were reversed and the level of epileptic activity lowered; meanwhile there was a marked decrease in the amplitude and frequency of discharges in the dependent foci (zones 1, 3, and 4) and a change in the polarity of the potentials. Activity in the foci then disappeared (Fig. 2C).

On repeated application of 0.2% strychnine solution to the coronary (area 1) and anterior sigmoid (area 3) gyri and also of a strychnine crystal to the orbital gyrus (area 2), alongside the area in which a focus had previously been suppressed by application of pentobarbital, a new epileptic complex was formed (Fig. 2D) with synchronized discharges in all its foci; the complex included an intact area of cortex, not treated with strychnine, which demonstrated generalization of the process. If the activity of one of the dependent foci was suppressed at this stage by application of pentobarbital, generalization of epileptic activity still continued and the complex continued to discharge by the same pattern as before (Fig. 2F).

It is impossible in this paper to describe many of the other features distinguishing relations between the foci thus created (this will be done in a special publication), and all that can be said is that in some cases activity was depressed in the primary foci after the formation of a new powerful focus. This phenomenon expressed essentially the dominance of the more powerful focus. Similar relations could arise in the early stages of formation of the complex and alternated with the manifestation of determinance of the hyperactive focus. Dominant-determinant relationships of this kind, incidentally, have been observed by the writers in whole brain preparations also.

The same relations between foci of increased activity are thus found in the isolated cortex as in the cortex of the intact brain [2-6]. In principle, the same relationships are formed between the determinant and dependent foci, and the formation of a single complex, whose pattern of activity is determined by the determinant focus, takes place in the same way. The determinant principle is thus realized in the cortex isolé also. What this means is that these relations between foci of hyperactivity are achieved through internal cortical mechanisms.

Meanwhile, the complex is formed more rapidly in the isolated cortex and generalization of the process is more marked, as is reflected in the spread of paroxysmal activity to unaffected regions of the cortex. As a rule this phenomenon is not found in the intact cortex. It can therefore be supposed that the basal structures have a modulating effect on the processes of formation of functional complexes in the cortex. It is an interesting fact that after reapplication of strychnine to a quiescent determinant focus, produced in the same way by strychnine, the newly arising activity may resemble acetylcholine discharges in its character. According to Ferguson and Jasper [10], the spike-wave and after-effect are generated by neurons in different layers of the cortex. If this conclusion is correct, it can be postulated that generalization of excitation consisting of a spike-wave and after-discharge from the determinant focus can take place horizontally, spreading along separate neuronal layers. The spread of discharges of reversed form from the determinant focus after application of pentobarbital to it can be examined from the same standpoint. This phenomenon also was observed in the intact brain, when acetylcholine was used to form a determinant focus [6]. In these same experiments strychnine evoked acetylcholine-like activity. It can be tentatively suggested that under cortex isolé conditions the recruiting of neurons in different layers of the cortex and the spread of excitation are facilitated.

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