DEVELOPMENT OF RECURRENT GENERALIZATION OF EXCITATION IN THE CEREBRAL CORTEX DURING CHANGES IN THE LEVEL OF ARTIFICIAL VENTILATION OF THE LUNGS

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During the study of the spread of paroxysmal excitation over the cerebral cortex after local application of strychnine, we found that the excitation may pass from the local cortical focus to the generalizing apparatuses of the subcortex. From here it may spread back again to the cortex, but this time it is generalized in character [2]. We have called this type of generalization "recurrent."

However, our experiments were carried out under urethane anesthesia, and as numerous experiments during recent years have shown, anesthetics which selectively block various subcortical formations may modify their interrelationship and interdependency to a considerable extent. Forbes's secondary response, for example, is known to appear only during deep nembutal anesthesia [3, 6]. Liu Chuan-kuei has found a new type of secondary response, which appears only under urethane anesthesia [7].

On the basis of these and many other similar facts, we are justified in postulating that urethane, by influencing the synchronizing apparatuses of the subcortex in some manner, makes it possible for recurrent generalization of paroxysmal excitation to occur. In order to confirm this hypothesis, further series of experiments on unanesthetized animals were required. The results of such experiments are described below in the present paper.

EXPERIMENTAL METHODS AND RESULTS

Acute experiments were carried out on adult unanesthetized rabbits. The animals received an intravenous injection of diplacin (tubocurarine), and were maintained on controlled respiration. A wide burr-hole was made in the skull under local anesthesia. In order to create an experimental local focus of excitation on the exposed surface of the cortex, a piece of filter paper (1 × 1 mm or 2 × 2 mm), soaked in 1% strychnine nitrate solution, was applied to the parietal region. The electrical activity of the strychninized area of the cortex and also the activity of the frontal, parietal and occipital regions of both cerebral hemispheres were recorded.

The experiment showed that with changes in the level of artificial ventilation of the lungs, the degree of generalization of the paroxysmal activity in the cerebral cortex varied (Fig. 1).

We shall analyze these facts at the end of the paper. At this moment we shall note simply that as a result of this series of experiments definite levels of ventilation were established corresponding to different degrees of generalization of the paroxysmal activity throughout the cerebral cortex. In other words, we could choose arbitrarily the degree of generalization of convulsive activity required in the course of the experiment. We used this method to induce convulsions during the study of the mechanisms of their spread over the whole surface of the cerebral cortex from a localized cortical area.

We may ask whether the convulsive attack is spread exclusively by intra- and intercortical connections, or whether it spreads as a result of active involvement of the subcortical structures in the process. The simplest way of finding the answer to this question was to separate the cerebral hemispheres by completely dividing the corpus callosum, applying strychnine locally to a part of one hemisphere, thereby causing a convulsion, and observing the changes in the opposite hemisphere while varying the degree of pulmonary ventilation. We carried out a series of experiments along these lines. The corpus callosum was divided 30-40 min before the beginning of the experiment

so that the animal was able to recover to some degree from the severe trauma. At the end of the experiment the animal was sacrificed, and the brain removed and fixed in formalin solution. The accuracy of the division was verified morphologically.

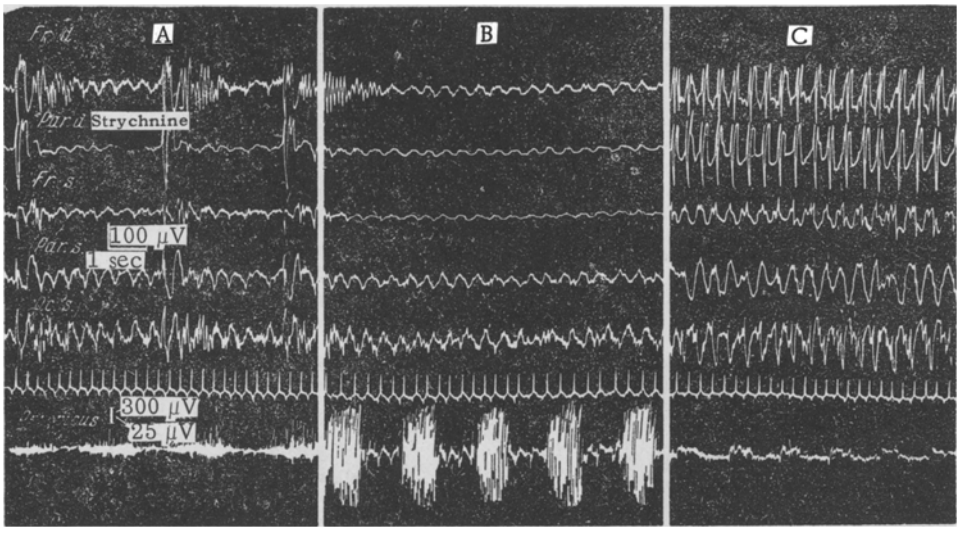

Fig. 1. Changes in the degree of generalization of strychnine excitation throughout the cerebral cortex depending on the level of artificial ventilation of the lungs. A) Normal ventilation, accompanied by comparatively infrequent, single, generalized paroxysmal volleys; B) disappearance of the paroxysmal excitation during asphyxia; C) development of a convulsive, generalized attack during the change to hyperventilation; Fr. d—right frontal region; Par. d—right parietal (strychninized point) region; Fr. s—left frontal; Par. s—left parietal; Oc. s—left occipital region; Phrenicus—potentials of the phrenic nerve.

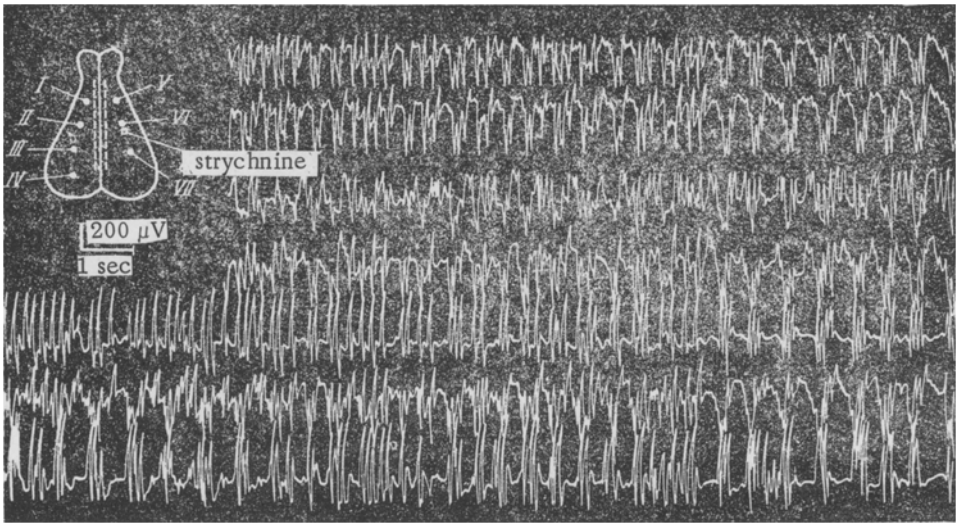

Fig. 2. Spread of a paroxysmal attack arising at a localized point on one hemisphere as a result of local application of strychnine over the whole surface of both hemispheres after complete division of the corpus callosum.

The experiments of this series showed that complete division of the corpus callosum does not prevent the spread of paroxysmal activity to the opposite hemisphere (Fig. 2). The process of generalization evidently takes place in this case as a result of the active involvement of the subcortical synchronizing apparatuses.

Which subcortical structures may perform the functions of these apparatuses? On the basis of our previous investigations and of reports in the literature, we postulated that one such structure could be the group of medial nuclei of the thalamus. It is in these structures that, according to various writers, the apparatuses for synchronization of the electrical activity of the cerebral activity are situated [4].

A special series of experiments in which the potentials were recorded from the nucleus centralis medialis of the thalamus, as the most typical nucleus of the thalamic reticular projection system, convinced us that this system plays an important role in the mechanism of recurrent generalization of paroxysmal activity. The potentials of the nucleus centralis medialis were recorded by means of nichrome electrodes (100 μ), drawn into a glass capillary tube. The electrodes were buried by means of a stereotaxic apparatus in accordance with the coordinates of Sawyer's atlas [9]. These experiments showed that during recurrent generalization of the convulsive activity throughout the cortex, and especially during the generalized convulsive attack, the activity of the nucleus centralis medialis underwent significant changes. Volleys appeared, synchronized with spikes arising at the site of application of the strychnine (Fig. 3). It must be pointed out that volleys appeared slightly sooner in the thalamus and were of greater amplitude than the synchronous volleys in the opposite hemisphere.

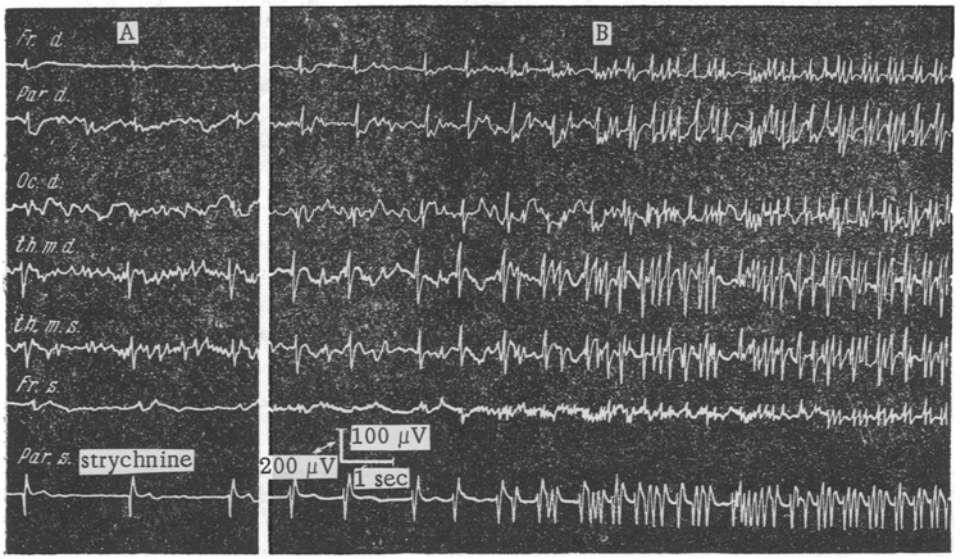

Fig. 3. Gradual development of the convulsive attack during hyperventilation. Paroxysmal volleys in the medial nuclei of the thalamus are more clearly defined than in the opposite hemisphere. A) Before hyperventilation; B) during hyperventilation; Fr. d—right frontal region; Par. d—right parietal region; Oc. d.—right occipital region; th. m. d.—right medial thalamus; th. m. s.—left medial thalamus; Fr. s.—left frontal region; Par. s.—left parietal region (point of application of strychnine).

It must be assumed that the medial nuclei of the thalamus are not the only system taking part in the formation of the recurrent generalization. Other mechanisms are possibly at work, for example, the reticular formation, and our subsequent investigations will deal with the discovery and accurate localization of these mechanisms.

We have previously remarked that, by changing the level of artificial ventilation of the lungs, we could either completely prevent the development of generalization of strychnine excitation from a local focus, or deliberately produce a powerful, generalized attack of paroxysmal activity, literally to order. What is the mechanism of the effect of a change in the volume of the pulmonary ventilation on the synchronizing apparatus of the subcortex? The results of these experiments suggest that the concentration of oxygen and carbon dioxide in the blood plays an important part in the transmission of these influences.

A qualitative estimate of the CO_2 and O_2 in the blood was obtained by recording the action potentials of the phrenic nerve.

We found in most experiments that with the respiratory center in a normal condition, characterized by volleys in the phrenic nerve indistinguishable from the activity associated with spontaneous respiration, generalized spikes were observed in the cortex (Fig. 1, A). During hypoventilation and asphyxia the respiratory center generated frequent and strong volleys; the paroxysmal volleys in the cortex became less frequent and in some cases disappeared altogether (Fig. 1, B). Finally, during weak hyperventilation, when a continuous stream of impulses passed along the phrenic nerve between the volleys, a convulsive burst developed in the cortex (Fig. 1, C). Hence the paroxysmal burst usually developed during slight hyperventilation. Particularly strong and prolonged bursts appeared during the change from hypercapnia to hyperventilation.

No direct experimental evidence is yet available to enable us to answer the question of why the burst should develop during slight hyperventilation. However, by comparing our experimental results with the data in the literature, we can postulate that it is in some way associated with the functional relationships between the desynchronizing and synchronizing apparatuses of the subcortex. In the earliest researches of Moruzzi and Magoun [8] it was found that stimulation of the desynchronizing divisions of the reticular formation depresses the activity of the synchronizing mechanisms of the thalamus. The depression of the activating structures liberates the synchronizing apparatuses [1]. Dell and co-workers showed that an excess of CO_2 in the blood causes strong excitation of the reticular activating system, whereas excess of O_2, on the other hand, depresses it [5].* Relationships of this type were evidently present also in our experiments.

This series of experiments demonstrates that the mechanism of recurrent generalization is evidently the universal mechanism of generalization of excitation in the cerebral cortex, and has nothing to do with the exceptional conditions of urethane anesthesia, although it is possible that in ordinary, natural pulmonary ventilation urethane anesthesia facilitates the activity of the synchronizing mechanisms of the brain stem.

While stressing the role of recurrent generalization of excitation in the cerebral cortex, our experiments, however, do not exclude the possibility that the spread of cortical excitation may also take place through intra- and intercortical connections, which presumably fulfill a more precise and specialized function in respect to the associative activity of the cortex.

SUMMARY

Acute experiments were staged on unanesthetized rabbits immobilized by diplacin. A study was made of the effect produced by the level of artificial pulmonary ventilation on generalization of paroxysmal excitation from the locally strychninized point of the cortex of large hemispheres along the whole cortical surface. As revealed, carbon accumulation in asphyxiated animals led to depression of paroxysmal charges. With subsequent hyperventilation there developed a generalized paroxysmal attack, involving both hemispheres. Section of the corpus callosum did not prevent the generalized paroxysmal attack. Experiments with employment of subcortical electrodes demonstrated that an important role in generalization of paroxysmal excitation along the cortex of large hemispheres is played by the medial group of hypothalamic nuclei, particularly by the contromedian nucleus.

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*As in the original Russian. The mention of the name of Dell most likely indicates that the conclusion expressed here is taken from [4] [Publisher's note].