22 persons investigated); they were found rarely (in only one of 12 patients) in Friedreich's ataxia.

Data of computerized tomography must be taken into consideration in the differential diagnosis between Friedreich's disease and the group of cerebellar degenerations, and this is of practical importance during medical genetic counseling.

Computerized tomographic signs of cerebellar atrophy were observed both in the initial stage of the disease and when gross disturbances of coordination were present.

In familial cases of cerebellar degenerations during investigation of several patients (members of the same family) computerized tomographic signs of cerebellar atrophy were found in all patients, but the severity of the changes differed in degree.

The differentiation of different degrees of severity of the disease according to the severity of the ataxic syndrome was confirmed by computerized tomography in patients with cerebellar degeneration of the I and II degrees of severity.

The investigation showed that computerized tomography can be effectively used for the diagnosis of some forms of hereditary-familial ataxias.

LITERATURE CITED

1. E. V. Shmidt, N. V. Vereshchagin, L. K. Bragina, et al., Zh. Nevropatol. Psikhiat., No. 1, 3 (1978).
2. E. V. Shmidt, N. V. Vereshchagin, L. K. Bragina, et al., Klin. Med., No. 9, 5 (1978).
3. J. Ambrose and G. Hounsfield, Br. J. Radiol., 46, 148 (1973).
4. R. Paxton and J. Ambrose, Br. J. Radiol., 47, 530 (1974).
5. E. F. Davidenkova and I. S. Liberman, Clinical Genetics [in Russian], Leningrad (1975), pp. 271-277.
6. P. E. Becker, in: Humangenetik (Stuttgart), 5, 1, 208 (1966).
7. R. T. C. Pratt, The Genetics of Neurological Disorders, London (1967), pp. 34-37.
8. J. F. Aita, Arch. Neurol. (Chicago), 35, 55 (1978).
9. S. Pogacar, M. Ambler, W. J. Conklin, et al., Arch. Neurol. (Chicago), 35, 156 (1978).
10. L. Pedersen and C. Gyldensted, Acta Neurol. Scand., 58, 81 (1978).
11. N. Z. Gurskaya, Zh. Nevropatol. Psikhiat., No. 6, 833 (1975).

BIOELECTRICAL CORRELATES OF PROTECTIVE MECHANISMS OF THE BRAIN*

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The study of the possibility of controlling the reserve and protective mechanisms of the brain is a promising theoretical trend in the development of new methods of treatment of diseases of the nervous system. So far as the control of brain reserves is concerned, besides pharmacologic methods great importance is also attached to therapeutic electrical stimulation [1-4], the oriented formation of new components of brain systems [5], and methods of adaptive biocontrol [6, 7].

Despite the importance of the use not only of reserve mechanisms, but also of the truly protective mechanisms of the brain, no significant progress has yet been made in this last field. Individual pronouncements and the results of research into the "protective" role of the slow waves of the EEG [8, 9] have not led to the formation of a corresponding theoretical approach.

The aim of this investigation was to seek ways of acting therapeutically on the brain that would be similar in principle with the intrinsic protective mechanisms of the brain itself, by studying the most likely bioelectrical correlates of these protective mechanisms.

The investigation was based on two assumptions.

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Local bioelectrical epileptogenesis is known to be, not the reflection of anatomical injury [10-12], but a response of the relatively intact brain.

1. It is assumed that stability of preservation or restoration of local epileptiform activity in the same brain zone is the result of local fixation of a response developing in long-term memory.

During sleep spreading paroxysmal activity is observed on the EEG of normal individuals, of patients with lesions of midline brain structures, and in many patients with severe forms of epilepsy. During the development of the disease slow waves become the predominant components of this paroxysmal activity.

2. It is assumed that at least one function of a neurophysiological process reflected on the EEG by local slow waves and by paroxysmal slow activity is disintegration of local and distant pathological connections, which explains the role of the mechanism of protection. Disintegration of connections related to normal brain activity naturally is also possible under these circumstances.

Two patients with multifocal epilepsy, diagnosed and treated by the use of implanted gold semimicroelectrodes with a working surface of between 0.01 and 0.15 mm^2, were studied.

The electrodes were connected into bundles so that each subsequent electrode ended 3-5 mm above its predecessor. Each bundle of electrodes was inserted through a separate burr-hole in the skull by a stereotaxic method, using a computer, and based on an idea suggested by Usov [13]. Later the method was developed by Anichkov [14] until it was, in principle, a novel technique and competitive with other stereotaxic methods. By this method it was possible to insert electrodes into assigned brain structures with a high degree of accuracy [15-17]. In view of the aim of the investigation to determine the precise location of epileptogenic zones and to discover zones suitable for therapeutic electrical stimulation, the electrodes were implanted into various thalamic structures (mainly the centrum medianum and the ventrolateral nucleus), the caudate nucleus, septum, tegmentum mesencephali, gyrus cinguli, various zones of the lateral surface of the cortex (mainly the temporal lobes), and other brain structures. The number of electrodes inserted into patient D. (male) was 88 and into patient B. (female) 42.

By means of a combined technique of investigation of the brain described previously [18-21] with implanted electrodes various parameters of brain activity were recorded, including during pharmacological, psychological, and certain other tests, and also before, during, and after electrical stimulation through the implanted electrodes.

In this investigation to depress the epileptogenic focus, a weak sinusoidal electric current not more than 0.01 μA in strength, with a voltage of 10-20 mV, and frequency 2 Hz was used as electrical stimulation; the duration of each period of stimulation from a G6-15 generator was 10 sec.

Altogether 10 sessions of stimulation were used on two patients. The reason why such a small number of cases is being published is because the results of stimulation and the practical importance of the technique used were consistently the same.

Zones of relatively intact activity and zones of marked rhythm disturbances with slow and epileptiform activity were recorded on the electrosubcorticogram (ESCoG) of patients D. and B.

The targets of stimulation were zones of epileptogenesis, characterized by stability and by a local type of epileptiform bioelectrical manifestations. Stimulation was aimed at one zone of the hippocampal gyrus, the uncus of the hippocampal gyrus, the pole of the temporal lobe, and the amygdala (Fig. 1). The main control consisted of ESCoG data, but in view of the importance of obtaining information on the degree of spread and the intensity of the changes which developed, the results of investigation of unit activity of neuronal populations (from the electrodes where it was recorded), evoked potentials, and slow electrical processes also were used as a control.

In patient D, the region of the pole of the left temporal lobe was exposed to a sinusoidal current with a frequency of 2 Hz and a voltage of 2 mV twice for 10 sec, with an interval of 13 min between applications. Immediately after stimulation, epileptiform activity disappeared in the zone where it was applied, and activity close to normal, and different from that recorded from neighboring electrodes, appeared (Fig. 2). The results of stimulation in other zones of this and the other patient depended directly on the initial

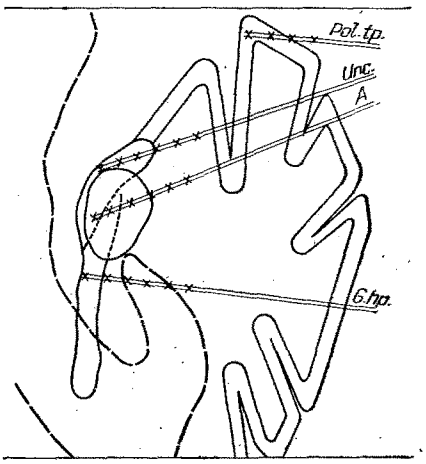

Fig. 1. Diagram of brain showing locations of electrodes (crosses) in deep brain formations. Pol. tp.) Pole of temporal lobe; Unc.) uncus of hippocampal gyrus; A) amygdala; G. hp.) hippocampal gyrus.

intensity of epileptiform activity. In patient B. electrical stimulation of this type, but with an intensity of 10 mV, was applied to the zone of most marked epileptiform activity in the region of the amygdala, then with an intensity of 20 mV in the region of the uncus of the hippocampal gyrus. After stimulation there was a marked and persistent decrease in the intensity of epileptiform activity (Fig. 3). Electrical activity in the zone of stimulation also differed from that recorded by neighboring electrodes, i.e., it reflected processes taking place locally in nerve tissue.

Spike discharges of neuronal populations were recorded in patient B. from many, but not from all, electrodes. In the region of stimulation no spike activity was found, but it was clearly present in the neighboring electrode of the same bundle, in the region of the uncus of the hippocampal gyrus, i.e., about 3 mm away. After stimulation, unit activity persisted in this neighboring electrode. Evoked potentials at the site of stimulation and in the region of the other electrodes showed no significant change (J. S. Peñalver Gonzales, laboratory data). Slow electrical activity immediately after stimulation showed no significant change (R. E. Kir'yanova, laboratory data).

A study of the ESCoG over a period of days and weeks show that although the level of local depression of the bioelectrical manifestations of epileptogenesis produced by electrical stimulation was preserved, the general pattern of brain electrical activity was modified after 3-5 days with the appearance of intensified epileptiform activity in another zone or zones of the brain. For instance, after stimulation of this kind applied to the amygdala, patient B. developed a persistent increase in epileptiform activity in the region of the uncus, and because of this stimulation was repeated. After 3-5 days the general pattern of slow electrical activity was reorganized in this patient, and the changes were least marked in the zone of stimulation.

The result achieved with a weak sinusoidal current is evidence that this method is an effective means of inhibiting the bioelectrical manifestations of epileptogenesis.

Normalization of the ESCoG or a decrease in the intensity of the bioelectrical manifestations of epileptogenesis but with preservation of the individual pattern of electrical activity in the region of stimulation can be regarded as evidence that the effect is achieved through abolition of the conditions required for manifestation of epileptogenesis, and not as a result of anatomical destruction of brain tissue. The procedure can thus be regarded as physiological in character, as a rather enhanced analog of the slow wave phenomenon that is characteristic of the brain.

Paroxysmal activity in epilepsy and certain other pathological processes may be of such amplitude that it goes beyond the bounds of microwave activity. The ratio between artificial slow waves and those observed in brain diseases thus does not exceed 1:10 or 1:20. The strength of the current measured in the course of stimulation varies within limits commensurate with intrinsic brain activity, in the region of 0.01:0.001 μA (S. G. Dan'ko, laboratory data). To understand how small an increase in the intensity of stimulation is needed to produce an effect, it may be recalled that during diagnostic electrical stimulation short electric pulses up to 20 V in voltage are used, and that diagnostic tissue polarization which, in the opinion of Walter and Crow [20, 21], is reversible stimulation, is produced by a waxing and waning direct current of 1 mA [22].

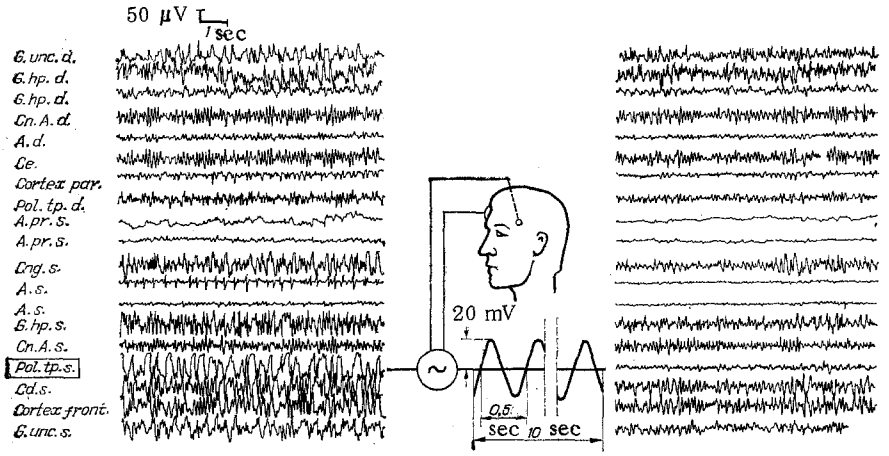

Fig. 2. Spontaneous ESCoG (left) and ESCoG after two sessions of unipolar stimulation by a weak sinusoidal current (in the course of 10 sec) to the region of the pole of the left temporal lobe in patient D. (on right). Block diagram of stimulation in center of figure. Local disappearance and a marked general decrease in epileptiform activity. G. unc. d.) Right uncus of hippocampal gyrus; G. hp. d) right hippocampal gyrus; Cn. A. d.) right hippocampus; A. d.) right amygdala; Ce.) gyrus cinguli; Cortex par.) right parietal cortex; Pol. tp. d.) pole of right temporal lobe; A. pr. s.) left anterior ventral thalamic nucleus; Cng. s.) left gyrus cinguli; A. s.) left amygdala; G. hp. s.) left hippocampal gyrus; Cn. A. s) left hippocampus; Pol. tp. s) pole of left temporal lobe; Cd. s.) left caudate nucleus; Cortex front.) left frontal cortex; G. unc. s.) uncus of left hippocampal gyrus.

The second important property of the suggested method is thus that the result achieved by electrical stimulation is commensurate with the physiological effect as regards both intensity and duration. A third most important property is the local character of stimulation, development of the effect in the zone of application of the current. Not only the ESCoG pattern, but also the firing pattern of neuron populations and the character of evoked potentials and of slow electrical processes are preserved at neighboring electrodes.

However, the late effect differed from the immediate effect. After depression of the region of marked epileptogenesis, a gradual increase in strength of epileptiform activity was observed on the ESCoG of epileptic patients in other, previously less epileptogenic, zones. For instance, depression of epileptiform activity in the region of the left amygdala in patient B. led within a few days to a marked increase in epileptogenesis in the region of the uncus of the hippocampal gyrus. These observations cannot be interpreted as the direct result of stimulation. They were due to a change in the state of the epileptogenic focus itself in the region of the amygdala, and they thus confirm yet again views on the role of the steady pathological state in brain diseases [18, 19, 23] and the need to take this factor into consideration, and they determine the place of the proposed new method, especially in epilepsy, as one element in a system of combined treatment. This combined treatment, in its general form, may now be made up of: 1) a change in the general conditions for functioning of the brain, or its general de-epileptization, achieved by pharmacological treatment or therapeutic electrical stimulation under biochemical control, 2) removal, if possible, of foci or anatomical destruction creating conditions for the appearance of foci or epileptogenesis, 3) the use of a new method, akin to physiological extinction of foci of epileptogenesis through implanted electrodes. The clinical possibilities of the suggested method have not yet been fully studied. The possibility cannot be ruled out that in the future it will be possible to select more or less local versions of this procedure and thus to combine the use of the reserve and protective mechanisms of the brain rationally in the patient's interests.

The neurophysiological mechanism of the effect of the method of destruction of the epileptogenic focus undoubtedly requires further elucidation. However, some data in this direction have already been published, including in publications by the present writer. The

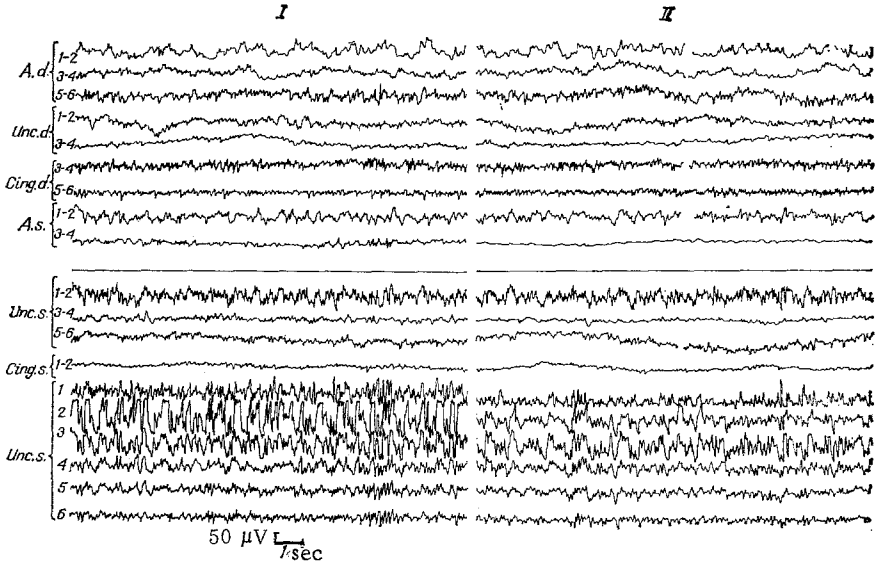

Fig. 3. Dynamics of ESCoG of patient B. before (I) and after (II) stimulation by weak sinusoidal current in region of uncus of left hippocampal gyrus (2nd and 3rd electrodes). A. d.) Right amygdala; Unc. d.) uncus of right hippocampal gyrus; Cing. d.) right gyrus cinguli; A. s.) left amygdala; Unc. s.) uncus of left hippocampal gyrus; Cing. s.) left gyrus cinguli.

results of oculography (L. N. Karpova, Departmental data) showed that not only during the period of development of typical spreading paroxysmal activity of the peak-wave type, accompanied by clinically recordable loss of consciousness, but also during the development of paroxysmal slow activity tracking a target is disturbed. A study of the functional anatomy of the brain of epileptics by the evoked potentials method revealed a disturbance, an interruption of connections in the zone of slow waves of the Δ-band [24]. Experimental studies of peak-wave activity conducted in several laboratories and, in particular, by Scherrer and Calvet [25], Verzeano [26], and others, have demonstrated characteristic and different changes in the state of neurons during the two phases of this phenomenon.

The original assumptions described in the introduction to this paper are to a large extent a working hypothesis. If, however, it is considered that at least one of the mechanisms of long-term memory is the formation and preservation of stable connections between neurons, with the possibility of subsequent reproduction of a state corresponding to connections of this character [27, etc.], and also that slow waves contributes to a reduction of the stability or potential activity of these connections, the original working hypothesis deserves further study. In this paper attention has been concentrated on spreading paroxysmal slow activity. However, there is no doubt that a similar role of local slow (delta!) waves must also be taken into account, although it is perfectly clear that spreading paroxysmal slow activity is a factor with a much more powerful action by virtue of its spreading nature alone.

The initial hypothesis must also be re-examined in another plane. As was pointed out in the introduction, slow-wave activity, especially paroxysmal, is ascribed a protective function although, naturally, the essential nature of slow activity is not confined to this function. The dynamics of paroxysmal activity, tested at frequent intervals during the development of the disease, reveals the progressive slowing and increase in amplitude of its components [28, etc.]; in epilepsy, moreover, direct correlation, of varied strength, has been found between the enhancement of local epileptogenesis and spreading paroxysmal activity. The impression is created that enhancement of paroxysmal activity is based on a principal analogous to positive feedback. Enhancement of local epileptogenesis is the cause of enhancement of paroxysmal spreading activity, which does not inhibit it because of the unfavorable strength ratio in the "epileptogenesis—protective forces of the brain" system. An electroencephalographic study of traumatic and other brain injuries shows that the developing epileptogenesis may disappear spontaneously, mainly evidently, because of a different strength ratio in the system mentioned above. However, enhancement of paroxysmal activity in the presence of an active focus of epileptogenesis reflects more than incompletely

effective protection. As follows from the same data cited above, it leads to a disturbance of brain functions. Enhancement of spreading paroxysmal activity and an increase in the amplitude and period of its components are evidence of transition of a physiological phenomenon into pathological, with all the consequences which that entails for brain activity. This example shows the relationship between physiological and pathological, and the dialectical unity and contradiction of protection and pathological reactions. Other aspects of the problem of protective reactions of the brain must evidently arise in the course of its further goal-directed study.

A new method of depression of epileptogenesis is suggested, based on the hypothesis that slow waves perform a protective function and, hence, that disintegration of epileptogenic foci by means of electrical stimulation simulating slow (paroxymal) activity is possible. Combined treatment of epilepsy, based on mobilization of the reserves of the brain and the use of procedures similar to its own protective mechanisms, opens up a number of new prospects in the clinical management of diseases of the nervous system and the future study of mechanisms of human brain activity.

LITERATURE CITED

1. N. P. Bekhtereva, A. N. Bondarchuk, V. M. Smirnov, et al., Vopr. Neirokhir., No. 1, 7 (1972).
2. N. P. Bekhtereva (N. P. Bechtereva), A. N. Bondarchuk (A. N. Bondartchuk), V. M. Smirnov, et al., Confin. Neurol. (Basel), 37, 136 (1975).
3. J. M. R. Delgado, Brain and Consciousness [Russian translation], Moscow (1971).
4. J. M. R. Delgado, in: Neurosurgical Treatment in Psychiatry, Pain, and Epilepsy, ed., W. H. Sweet, S. Obrador, and J. G. Martin-Rodriguez, Baltimore (1977), p. 615.
5. V. M. Smirnov and Yu. S. Borodkin, Fiziol. Cheloveka, 1, No. 3, 525 (1975).
6. N. V. Chernigovskaya, A. S. Tsukerman, and S. A. Movsisyants, Byull. Eksp. Biol. Med., No. 1, 32 (1974).
7. N. V. Chernigovskaya, I. L. Knorozova, S. A. Movsisyants, et al., Fiziol. Cheloveka, 1, No. 6, 1070 (1975).
8. W. Grey Walter, The Living Brain, London (1953).
9. N. P. Bekhtereva and A. N. Orlova, in: Proceedings of the 1st Interregional Conference of Neurosurgeons of Western Siberia and the Urals [in Russian], Novosibirsk (1957), p. 113.
10. W. H. Calvin, Brain Res., 39, 71 (1972).
11. A. R. Wyler, E. E. Fetz, and A. A. Ward, Exp. Neurol., 40, 567 (1973).
12. A. R. Wyler and E. E. Fetz, Exp. Neurol., 42, 448 (1974).
13. V. V. Usov, in: Deep Structures of the Human Brain under Normal and Pathological Conditions [in Russian], Moscow–Leningrad (1966), p. 176.
14. A. D. Anichkov, Inventor's Certificate 486744 (USSR).
15. A. D. Anichkov, Fiziol. Chelovska, 3, No. 2, 372 (1977).
16. A. D. Anichkov and Yu. Z. Polonskii, Fiziol. Cheloveka, 3, No. 2, 379 (1977).
17. Yu. Z. Polonskii, Fiziol. Cheloveka, 3, No. 2, 376 (1977).
18. N. P. Bekhtereva, Neurophysiological Aspects of Human Psychological Activity [in Russian], Leningrad (1971).
19-21. N. P. Bekhtereva, Neurophysiological Aspects of Human Phychological Activity, 2nd Edition [in Russian], Leningrad (1974).
22. N. P. Bekhtereva, A. N. Bondarchuk, V. M. Smirnov, et al. Physiology and Pathophysiology of Deep Structures of the Human Brain [in Russian], Leningrad–Moscow (1967).
23. N. P. Bekhtereva, in: Neurophysiological Principles of Normal and Pathological Reactions of the Human Brain [in Russian], Leningrad (1970), p. 7.
24. D. K. Kambarova and F. I. Kolosov, Fiziol. Cheloveka, No. 2, 202 (1977).
25. J. Scherrer and J. Calvet, in: Synchronization of EEG Activity in Epilepsies, H. Petsche and M. A. B. Brazier, eds., Vienna (1972), p. 112.
26. M. Verzeano, in: Synchronization of EEG Activity in Epilepsies, ed. H. Petsche and M. A. B. Brazier, Vienna (1972), p. 154.
27. M. N. Livanov, Usp. Fiziol. Nauk, 6, No. 3, 66 (1975).
28. N. P. Bekhtereva, Biopotentials of the Cerebral Hemispheres in Supratentorial Tumors [in Russian], Leningrad (1960).