CORRELATION BETWEEN THE EEG AND CORTICAL UNIT ACTIVITY DURING DEVELOPMENT OF AN EXPERIMENTAL BRAIN TUMOR

N. A. Arkhipova

UDC 616.831-006-092.073.97

During growth of an experimental brain tumor (astrocytoma) general and local changes in the EEG increase in intensity. During the development of a superficial tumor there is a decrease in amplitude of the potentials and dominance of the EEG by the theta-rhythm; no clear local disturbances of the potentials were detected. During the development of an intracerebral tumor three stages of changes were distinguished in the dynamics of the EEG: I) absence of local disturbances, presence of diffuse Δ-activity and epiactivity; II) the appearance of interhemispheric asymmetry with a focus of pathological electrical activity; and III) sharp inhibition of rhythmic activity in all regions. Corresponding with the severity of the changes in the EEG, changes were also observed in unit activity: a decrease in the number of spontaneously active neurons and a decrease in the mean frequency of spontaneous unit discharges on account of the predominance of slow-firing neurons.

Investigations [1, 5, 9, 12] have demonstrated the great importance of the EEG in the diagnosis of local lesions of the human brain. However, despite extensive clinical use of the EEG, it is extremely difficult to follow the dynamics of electrical phenomena in patients during the development of a tumor. Descriptions of individual investigations of brain activity during the development of experimental tumors have been given in the literature [2, 3, 11] but only changes in the EEG are mentioned. By the study of experimental tumors not only can the dynamics of the changes in brain activity be investigated, but some of the mechanisms at the basis of those changes can be elucidated. A promising step toward the solution of this problem is the study of correlation between the EEG and single unit activity.

The object of the investigation described below was to examine the dynamics of the EEG and of cortical unit activity at various stages of growth of an experimental tumor (astrocytoma) in rabbits.

EXPERIMENTAL METHOD

A dedifferentiated astrocytoma obtained by L. Ya. Yablonovskaya and A. P. Avtsyn in 1963 was transplanted into the brain of experimental rabbits. The tumor cells were transplanted in the laboratory of experimental histopathology, Institute of Human Morphology, Academy of Medical Sciences of the USSR by the method described by Yablonovskaya [8]. The tumor was transplanted into the right parietal region of 3 or 4 animals at a time. Electrophysiological phenomena were recorded from the 25th to the 85th day after transplatation of the tumor cells at intervals of 2-3 days. To determine the character of the morphological changes the brains of the rabbits, killed at the end of the experiment, were investigated histologically. Rabbits in which the tumor did not develop were used as the controls. During the experiments the EEG and single unit activity were recorded simultaneously. Electrodes for recording were located at symmetrical points of the affected and healthy hemispheres over the sensomotor and visual areas. The reference electrode was fixed to the ear. Unit activity in the visual cortex was recorded with glass microelectrodes filled with 3M KCl or 4M NaCl. The recording technique was described in greater detail previously [4]. Alto-

Laboratory of Neurophysiology, Institute of Neurosurgery, Academy of Medical Sciences of the USSR, Moscow. Laboratory of Experimental Histopathology, Institute of Human Morphology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 76, No. 7, pp. 17-20, July, 1973. Original article submitted October 25, 1971.

© 1974 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for $15.00.

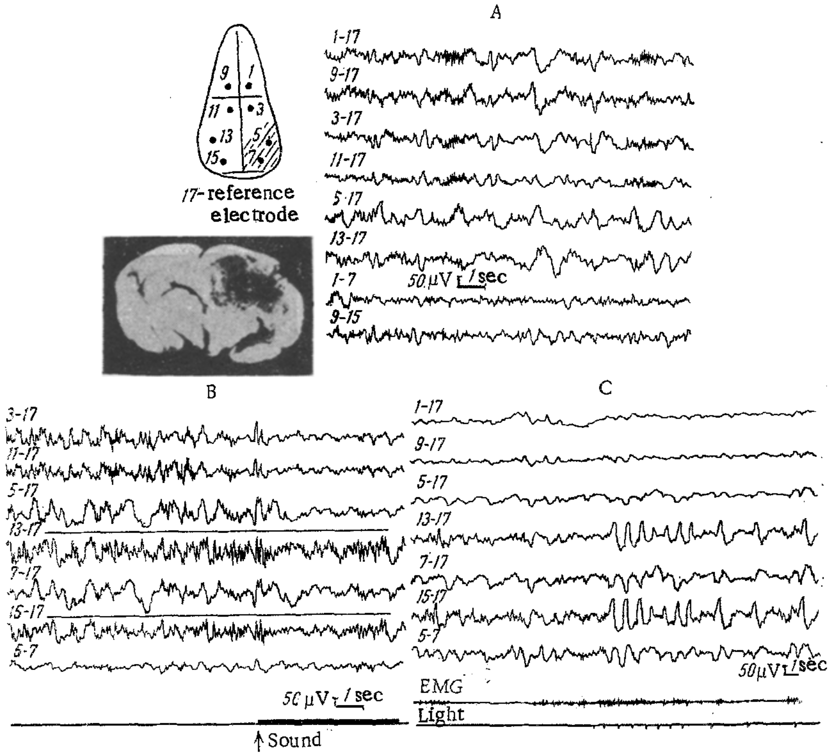

Fig. 1. Increase in general and local changes in EEG of a rabbit during development of experimental brain tumor. Top left – general view of rabbit's brain with tumor. Unstained preparation. A large tumor showing the right lateral ventricle and infiltrating the centrum semiovale, hippocampus, and part of the temporal cortex, was found in the brain 83 days after transplantation of the tumor. Brain stem severely compressed and shifted to the left. A) EEG 22 days after transplantation of tumor; B) EEG 39 days after transplantation of tumor; C) 83rd day after transplantation of tumor.

gether 72 experiments were performed on 25 rabbits. Activity of 324 neurons was recorded. The tumor took successfully in 19 of the 25 rabbits. Activity of 198 neurons was recorded in the rabbits with tumors.

EXPERIMENTAL RESULTS

In the analysis of the material, two groups of observations could be clearly distinguished. Group 1 were made on three rabbits with superficial tumors located epidurally and not invading the cortex, or affecting only its first and second layers in a few cases. Group 2 were made on 16 rabbits with intracerebral tumors of different sizes and in different places.

The EEG of the rabbits of group 1, tested between the 42nd and 67th days after transplantation of the tumor cells, showed a decrease in amplitude of the potentials, fast waves with preservation of regional differences, and a stable theta-rhythm. A superficial structure, even if of considerable size, as a rule produced no clear local disturbances of the EEG. A stable theta-rhythm on the rabbit EEG is known to be characteristic of the response to stress [6]. This state of increased excitability was also manifested by the appearance of reflex movements to inadequate stimuli (photic, acoustic). Electrophysiological investigation of the rabbits of group 2 (with intracerebral tumors) showed three stages of the EEG changes. In stage I the local changes in the biopotentials were not yet clearly marked; individual Δ-waves and pointed waves of epileptoid character were recorded diffusely (Fig. 1A). Evoked potentials to photic stimulation at symmetrical points of the affected and intact hemispheres were similar in shape and amplitude. Rhythm binding to flashes appeared mainly at frequencies of 3-5 flashes/sec. Stage II of the EEG changes was character-

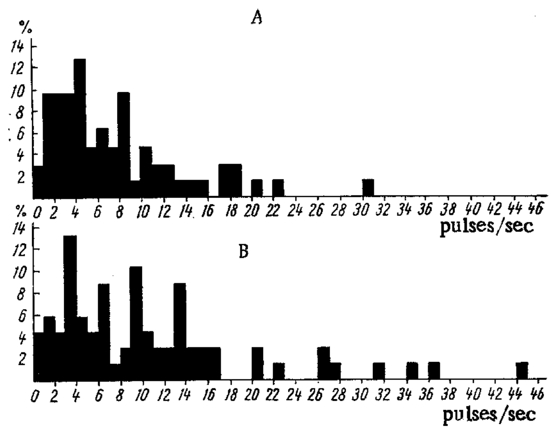

Fig. 2. Relative distribution of neurons by mean firing rate in the presence of a focus of pathological activity (A) and in the normal cortex (B). Abscissa, mean spontaneous firing rate of neurons; ordinate, number of neurons (in %).

ized by the appearance of interhemispheric asymmetry with a focus of pathological activity in the zone of growth of the tumor (Fig. 1B). In the region of the cortex surrounding the tumor unstable slow waves, increasing in response to afferent stimulation, were recorded. At the same time the latent period of the evoked potential to photic stimulation was increased, as also was the duration of its positive-negative complex. In response to repeated afferent stimulation, the local disturbances of the potentials against the background of general activation were less well defined. In stage III of the electroencephalographic manifestations of tumor development a generalized decrease in amplitude of the potentials and slowing of the cortical rhythm were observed. The activation response to afferent stimulation was weak. Evoked potentials, like the rhythm-binding response, either were absent or were seen extremely irregularly, and in a reduced form (Fig. 1C). These changes in the EEG were stable and irreversible during function tests. The changes in unit activity corresponded in severity to the changes in the EEG.

In this investigation only the spontaneous unit activity was considered. During an increase in severity of the pathological changes in the EEG, the number of spontaneously active neurons diminished. In four rabbits in which growth changes were observed in the EEG potentials, unit activity could not be recorded at all (in these rabbits the tumor invaded the occipital cortex). Parallel with the decrease in the number of spontaneously active neurons, a decrease in the mean spontaneous firing rate of the neurons was observed. In the control rabbits the mean spontaneous firing rate of the neurons of the visual cortex under the experimental conditions was 10.6/sec. In the rabbits with tumors, in the presence of marked slow activity (stages II and III) it was 7.3/sec. The decrease in the mean spontaneous firing rate occurred on account of the predominance of cells discharging at low frequency. As Fig. 2A shows, in rabbits with tumors about 50% of neurons discharged at a frequency below 5/sec; in the control animals (Fig. 2B) this firing rate was observed in 30% of neurons. In the normal visual cortex 12% of neurons discharged at frequencies higher than 20/sec, while in the presence of a tumor and against the background of slow pathological activity, only 4.6% of neurons discharged at this frequency.

Comparison of the electrophysiological data with the results of morphological examination of the brain revealed correlation between the degree of development of the tumor and the disturbances of electrical activity of the brain. Stage I of the electrophysiological changes was observed in rabbits with a small tumor located deep in the hemisphere or on its surface. Stage II of the EEG changes corresponded to the presence of a large and extensive tumor invading the walls of the lateral ventricle and compressing the basal ganglia. Marked generalized changes in the potentials (stage III) were characteristic of a tumor in the late periods of its development, when it occupied almost the whole hemisphere, caused severe compression of the brain stem, and invaded the opposite hemisphere. Under these circumstances, partial degeneration of the afferent fibers running to wide areas of the cortex, including those investigated, was observed. The decrease in the mean spontaneous firing rate of the neurons discovered in these experiments corresponds to that detected in preparations of the neuronally isolated cortex [7]. The hypothesis that subcortico-cortical connections play an important role in the maintenance of spontaneous cortical activity was thus confirmed. However, besides the deafferentation factor, a role in the genesis of the disturbances of the EEG and single unit activity cannot be ruled out for changes in the brain tissue due to disturbance of the circulation, edema, and compression, and also for changes in the normal ratio between glia and neurons, leading to changes in the metabolism of the nerve tissue [10].

LITERATURE CITED

1. N. P. Bekhtereva, Cerebral Biopotentials in Supratentorial Tumors [in Russian], Leningrad (1960).
2. I. N. Dimant, Experimental Tumors of the Central Nervous System [in Russian], Tashkent (1966).
3. B. N. Isamukhamedov, The Study of the Dynamics of the EEG during Development of a Glial Tumor Transplanted into the Brain and at the Stages of Radiation-Induced Carcinogenesis in the CNS. Author's abstract of candidate's dissertation, Tashkent (1969).

4. V. E. Maiorchik and N. A. Arkhipova, Fiziol. Zh. SSSR, No. 8, 793 (1969).
5. V. E. Maiorchik, Clinical Electrocorticography [in Russian], Leningrad (1964).
6. L. A. Novikova and D. A. Farber, Fiziol. Zh. SSSR, No. 11, 1293 (1959).
7. M. M. Khananashvili and É. G. Zarkeshev, Fiziol. Zh. SSSR, No. 10, 1329 (1970).
8. L. Ya. Yablonovskaya, Experimental Brain Tumors Obtained by Heterotransplantation and Induction [in Russian], Leningrad (1967).
9. Y. H. A. van der Drift, The Significance of Electroencephalography for the Diagnosis and Localization of Cerebral Tumors, Leiden (1957), p. 1.
10. Y. Herzog, W. A. Levy, and L. C. Schenberg, J. Neuropath. Exp. Neurol., 24, 153 (1965).
11. Y. Tomka, A. Sarcadi, and S. Zettner, Ideggyogyàszati, Szemle, 23, 4 (1970).
12. W. G. Walter, Lancet, 231, 305 (1936).