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FORMATION OF A GENERATOR OF PATHOLOGICALLY ENCHANCED EXCITATION IN THE CAUDATE NUCLEUS IN AN EXPERIMENTAL PARKINSONIAN SYNDROME

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KEY WORDS: tetanus toxin; generator of pathologically enhanced excitation; parkinsonian syndrome; caudate nucleus.

Local disturbance of inhibitory mechanisms in the rostral part of the two caudate nuclei after microinjection of tetanus toxin (TT) leads to the development of a number of neuropathological syndromes in animals [1, 3, 4] which are based on the appearance of corresponding hyperactive determinant structures [3]. In the late stages of the pathological process the animals develop a parkinsonian syndrome. The investigations so far undertaken have suggested that the character of the neurochemical organization of the hyperactive determinant structure in this syndrome is linked with activation of the cholinergic mechanisms of the caudate nuclei in connection with a disturbance of dopaminergic control under the influence of TT.

Disinhibited cholinergic interneurons of the caudate nuclei may perhaps form a generator of pathologically enhanced excitation [3], which may be the working neuropathological component of the determinant structure of this syndrome. To test this hypothesis, the character of unit activity in the rostral part of the caudate nuclei was studied in rats with such an experimental parkinsonian syndrome.

EXPERIMENTAL METHODS

Experiments were carried out on male albino rats weighing 250-270 g. Microinjections of TT were given into both caudate nuclei in accordance with coordinates taken from the stereotaxic atlas [9]: AP −2.0, L 2.5, H 4.0 mm, by the method described previously [4]. Spontaneous activity of the neurons was investigated under chloral hydrate anesthesia (350 mg/kg). To record unit activity metal electrodes with viniflex insulation (diameter of tip 10-15 μ) were used. Spontaneous unit activity was investigated in three tracks (Fig. 1A) in the caudate nuclei on the right side, located in frontal plane AP −2.0 mm, extending in depth from 3.5 to 4.9 mm and with a distance apart in the mediolateral direction of 200 μ coordinates L 2.3, L 2.5, L 2.7 mm). In each track spontaneous unit activity was evaluated at 15 points situated 100 μ apart in the vertical direction. Passage from one point to the next occupied 20 sec, and during the next 50-55 sec the presence or absence of spontaneous activity (single, grouped, rhythmic) was determined. If activity was present the point was considered to be active and potentials were recorded on magnetic tape for 180 sec. In each series (animals with experimental parkinsonian syndrome, intact rats, and control animals receiving an injection of inactivated TT 5 days before the investigation, at the same times as the experimental animals) 180 points were tested. To characterize the changes in spontaneous activity the number of active points, their distributions depending on depth in the track, the character and frequency of the discharge of single neurons, the character of distribution of the neurons depending on frequency, and the mean firing rate of the neurons in each series of the investigation were determined. A M-4 cathode follower, VC-9 oscilloscope, ATAC 501-20 analyzer (from Nihon Kohden, Japan), and a Jupiter tape recorder were used.

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TABLE 1. Mean Values and Standard Deviations of Firing Rate of Caudate Neurons in Animals of Different Groups

Group of animals	Number of neurons	Firing rate, spikes/sec	σ
Intact	73	0,49±0,09	0,7689
Control	26	0,82±0,14	0,7216
With parkinsonian syndrome	7	3,6±0,97	8,23

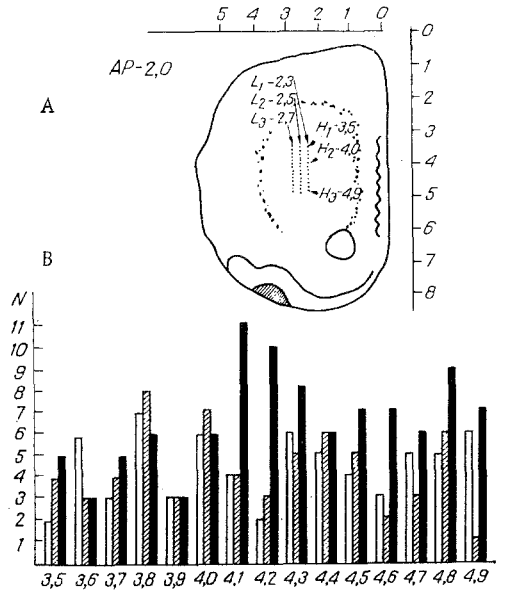

Fig. 1. Scheme (A) of frontal section through region of brain passing through head of caudate nucleus and showing arrangement of tracks, and histogram (B) of distribution of number of active points at different levels of tracks. Abscissa, levels of track (in mm); ordinate, number of active points. Black columns represent number of active points in animals with parkinson syndrome, obliquely shaded columns — in control animals, unshaded — in intact animals.

EXPERIMENTAL RESULTS

The distribution of the absolute number of active points by depth in the track is shown in the histogram in Fig. 1B. In rats with a parkinsonian syndrome the number of active points at a depth of 4.1-4.9 mm was considerably greater than in the intact and control animals. The greatest differences were found at depths of 4.1 and 4.2 mm, i.e., in the region of injection of TT in the experimental animals.

In the intact rats (Fig. 1B) active neurons were found in 37.2% of points tested, made up of 11.6% of active points at depths of 3.5 to 4.0 mm and 26.6% at depths of 4.1-4.9 mm. In the control animals injected with inactivated TT spontaneously active neurons were found at 32.5% of points tested, and their distribution at the two levels mentioned above was 12.2 and 20.0% respectively. In animals with a parkinsonian syndrome the number of active points was 55.5%, with 12.2 and 42.4% respectively at the levels indicated above.

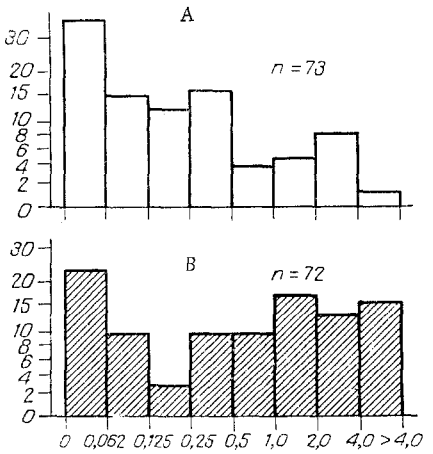

Fig. 2. Distribution of caudate neurons by spontaneous firing rate in intact animals (A) and animals with parkinson syndrome (B). Abscissa, frequency (spikes/sec); ordinate, number of neurons (in %).

In animals with a parkinsonian syndrome, neurons with a relatively high discharge frequency were found at most of the points tested, but were not present in the control animals (Table 1).

Analysis of the distribution of the neurons by discharge frequency showed (Fig. 2) that the number of neurons with a relatively high frequency of spike generation (1.0 spike/sec or more) in the region studied was increased. Changes in unit activity of the same kind were described previously, after the formation of generators of pathologically enhanced excitation in other parts of the CNS after local injection of TT into them [3].

Factors causing a decrease in the dopamine concentration in caudate nuclei (chronic administration of reserpine, injury to the nigrostriatal bundle), which are manifested phenomenologically as an experimental parkinsonian syndrome, are known to increase the frequency of spontaneous and evoked activity of caudate neurons [11, 12, 14, 15]. These facts are interpreted as the result of disinhibition of cholinergic neurons of the caudate nuclei, which are under inhibitory tonic dopaminergic control [7, 8, 10, 13]. The writers showed previously [1] that intrastriatal microinjections of dopamine and of atropine, which blocks cholinergic mechanisms, lead to considerable depression of the principle symptoms of parkinsonism in rats evoked by microinjection of TT. This suggests that the operant part of the generator of pathologically enhanced excitation consists of cholinergic neurons of the caudate nuclei, disinhibited through disturbance by TT of dopaminergic mechanisms.

An increase in the frequency of spontaneous and evoked unit activity in the caudate nuclei also has been obserbed by other workers [12, 14] in the initial stage of experimental parkinsonism caused by injury to the dopamine system. These investigations also showed that the level of enhanced activity later falls, to reach values close to normal after a few weeks or months. One year after injury to the nigrostriatal bundle, when dopamine was almost completely absent in the nucleus, no increase in firing rate of the neurons was found [12]. The question accordingly arises: What neuropathological mechanism lies at the basis of the parkinsonian syndrome in its late stages? The present investigation showed that in rats with a parkinsonian syndrome an increase in the number of spontaneously active neurons coincided with an increase in the firing rate of the neurons. This phenomenon was found also after chemical destruction of the nigrostriatal dopamine system [16] in the stage of marked signs of akinesia and rigidity. The increased number of spontaneously active neurons may perhaps bring about a state of hyperactivation and create the neuropathophysiological basis for a generator of pathologically enhanced excitation in the caudate nuclei in the late stages of development of the parkinsonian syndrome. On the theoretical level there is one other possible explanation for the development of neuropathophysiological changes in the late stages of development of the parkinsonian syndrome, namely acquisition of the properties of hyperactive determinant structures by other formations related to the mechanisms of hyperkinesia. Evidence in support of this possibility is given by the results of a study of the activity

and effects of stimulation of brain structures in parkinsonism [2]. Phenomena of this type have been described in connection with experimental multifocal epilepsy [3] and the behavior of secondary mirror foci [5, 6].

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FUNCTIONAL ACTIVITY OF PLATELETS IN THE EARLY PERIOD AFTER ARTIFICIAL HEART IMPLANTATION

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KEY WORDS: platelets; adhesion; aggregation; fibrinogen; artificial heart.

Platelets play an active part in hemostasis [5, 6, 8, 9, 12] and, because of their specific property of adhesion, they are the first blood elements to react to changes arising in the blood vessels [8, 11, 12].

Since the role of platelets and their adhesion-aggregation properties after implantation of an artificial heart have not been studied, it was decided to remedy this deficiency.

EXPERIMENTAL METHODS

Experiments were carried out on 10 calves weighing 90-100 kg into which artificial hearts of Soviet manufacture were implanted. To determine the state of the platelets methods of ad-

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