PATHOGENETIC FACTORS OF EXPERIMENTAL PHOTOGENIC EPILEPSY

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The character of formation of an experimental syndrome of photogenic epilepsy, obtained by creating a generator of pathologically enhanced excitation in the lateral geniculate body by local injection of tetanus toxin, was studied in chronic experiments on rats. The initial manifestations appearing in the animals were shown to be due to pathological enhancement of specific sensory excitation in the lateral geniculate body and to be accompanied by a marked increase in amplitude of the evoked potential in the visual cortex. The subsequent development of a neuropathological syndrome was connected with diffuse disturbances of rhythmic electrical activity of the brain, characteristic of a state of increased epileptic predisposition in the experimental animals. The results of these experiments indicate an important role of specific and nonspecific factors of epileptogenesis in the formation of experimental photogenic epilepsy.

KEY WORDS: Photogenic epilepsy; lateral geniculate body; generator of pathologically enhanced excitation; tetanus toxin.

A previous investigation [4] showed that the formation of a generator of pathologically enhanced excitation (GPEE) in the lateral geniculate body (LGB) after local injection of tetanus toxin (TT) into this nucleus leads to the formation of a syndrome of photogenic epilepsy in the experimental animals. The study of this syndrome suggested that an important role in its formation is played by changes both in specific mechanisms of conduction of the sensory visual stimulus and by nonspecific mechanisms of cerebral electrogenesis.

The object of the present investigation was to study the pathogenetic role of the above-mentioned mechanisms in the formation of experimental photogenic epilepsy.

EXPERIMENTAL METHOD

Chronic experiments were carried out on male albino rats weighing 250-300 g. To produce the GPEE, TT was used (activity of TT 5×10^5 mouse MLD/ml). To inject TT into LGB of the right hemisphere and to implant the subcortical electrodes, a stereotaxic technique was used. The technique of the operation was described in [4].

To record the electroencephalogram (EEG) and electromyogram (EMG) of the rats during generalized epileptic fits special hammocks fixing the trunk but not restricting movement of the head, limbs, and tail were used. Preliminary experiments showed that this method of fixation of the animals leads to no undesirable changes in the evoked responses in brain structures, in agreement with observations by other workers [7]. For analysis, the evoked potentials were averaged on the ATAS-501-20 computer (Japan). During the period of averaging the animals were presented with 50 stimuli at a frequency of 0.3/sec. Pauses between averaging periods were 5 min in duration. The flash tube was placed 25 and 30 cm from the animal's eyes and the intensity of illumination was 45 lx. In each experiment the location of the tip of the micropipet and subcortical electrodes was verified morphologically.

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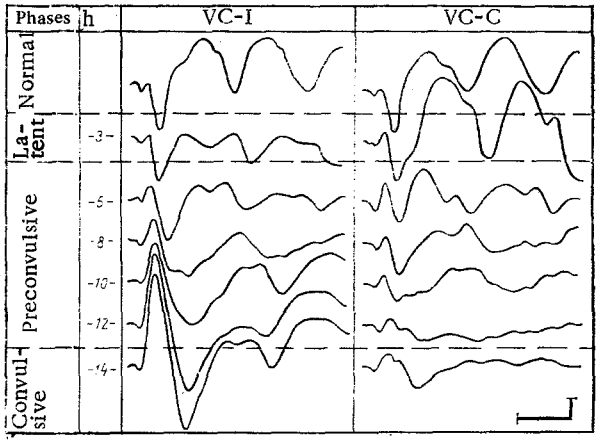

Fig. 1. Changes in evoked potentials in visual cortex at various times after injection of tetanus toxin into lateral geniculate body. VC-I) Ipsilateral and VC-C) contralateral regions of visual cortex relative to LGB into which TT was injected. Calibration: amplitude 150 μV, duration 100 msec.

EXPERIMENTAL RESULTS

The first sign of formation of a neuropathological syndrome of photogenic epilepsy in the rats after injection of TT into LGB was a change of photoreactivity in the LGB—visual cortex system [2, 4]. The greatest changes in amplitude were found in the first component of the evoked potential in the visual cortex on the side of formation of GPEE in LGB (Fig. 1). This wave gradually increased in amplitude and was usually many times greater than the corresponding evoked potentials both under normal conditions and in the contralateral visual cortex in different phases of the neuropathological syndrome. A special analysis of associated changes in evoked activity in LGB (after injection of TT into it) and in the ipsilateral region of the visual cortex, undertaken previously [2], showed that the changes in reactivity of the visual cortex were due to pathological enhancement of specific sensory excitation in LGB as a result of the formation of a GPEE in it.

At the later stages of development of the syndrome, besides the changes in photoreactivity in the cortical projection region described above, a pathological enhancement of vasomotor reactivity also was observed in the animals and was expressed as the appearance of characteristic compulsive motor responses to the photic stimulus. These compulsive responses were manifested as retro- and laterocursive movements appearing in response to single photic stimuli and also as on- or off-responses to high-frequency photic stimulus ($\geq$ 30 Hz) (Fig. 2). A distinguishing feature of the responses of this type was their lateralized character: As a rule compulsive movements appeared in response to illumination of the contralateral eye relative to the LGB in which the GPEE was formed, and the movements themselves were directed toward the side of that LGB. This fact may indicate the great importance of the specific visuomotor pathway, including the ventral nucleus of LGB as one of its components, in the triggering of compulsive motor responses [6, 10, 14]. The predominantly monocular triggering of these responses can be explained by the almost complete decussation of fibers in the optic chiasma in rats [8].

In the next stage of development of the pathological process, epileptic fits began to be provoked by flashes or to arise spontaneously. In this period alternation of synchronization and desynchronization of EEG activity was observed. This alternation of high-amplitude low-frequency activity and of low-amplitude high-frequency activity could be spontaneous (Fig. 3A) or could be evoked by photic stimulation (Fig. 3B, C). In the initial period after the onset of epileptic paroxysms desynchronization of EEG activity led to stabilization of reactivity of the visual structures to the photic stimulus: In this case a nongeneralized evoked potential, not increased in amplitude, appeared in response to repetition of the flash (Fig. 3B). However, in the late stages of the syndrome a flash presented against the background of established desynchronization could evoke a hypersynchronized, generalized afterdischarge (Fig. 3C).

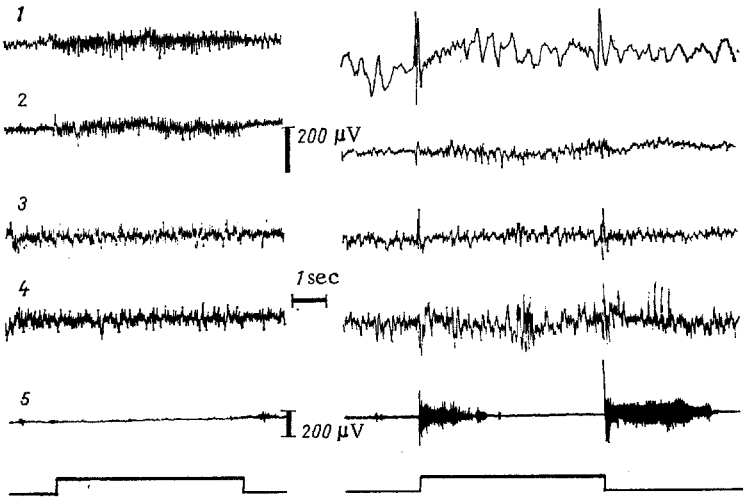

Fig. 2. Photogenic compulsive movement in rats as on- and off-responses to repetitive photic stimulation. Record on left made 2 h 20 min, and on right 12 h 40 min after injection of TT into right LGB. 1) Right, 2) left visual cortex; 3) right; 4) left LGB; 5) extensor of hind limb. Deflection of horizontal line below trace upward and downward corresponds to on and off of repetitive photic stimulation with frequency of 30 Hz.

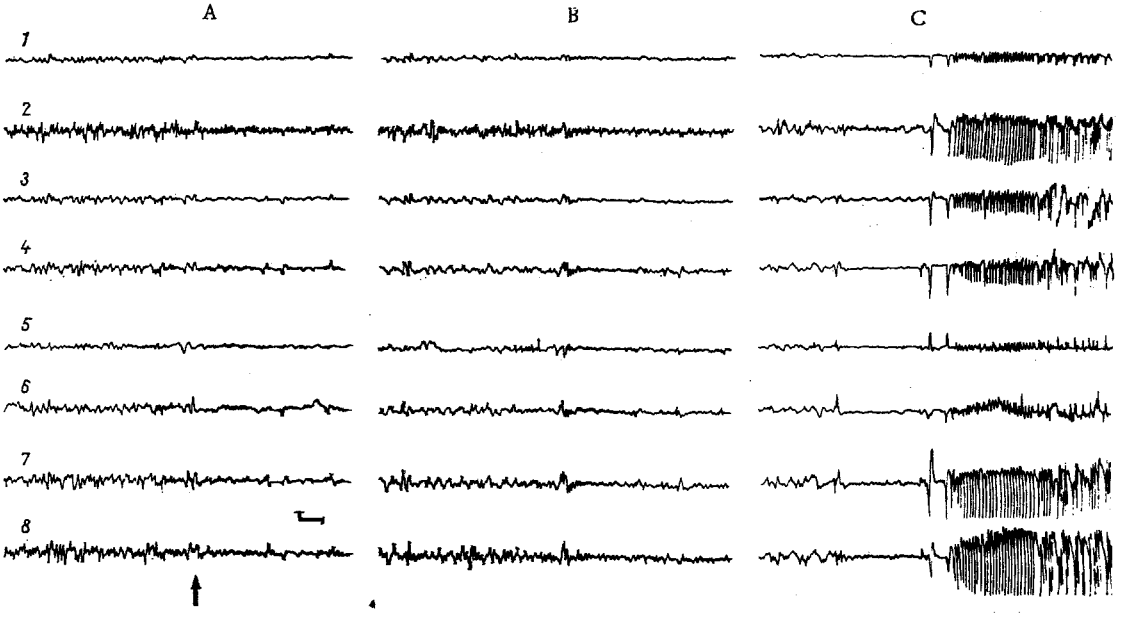

Fig. 3. Alternation of synchronization and desynchronization of EEG activity in between fits during convulsive phase. A) Spontaneous desynchronization of background EEG (time of desynchronization indicated by arrow below trace); B) desynchronization of background activity following high-amplitude generalized evoked response to first flash; C) hypersynchronized epileptic after-discharge evoked by flash against background of established desynchronization. Records A and B obtained 15 h, and C 19 h after injection of TT into right LGB. 1) Basal amygdaloid nucleus; 2) ventral hippocampus; 3) left pontine reticular nucleus; 4) unidentified zone of thalamus; 5) right sensomotor cortex; 6) right visual cortex; 7) right LGB; 8) left LGB. Calibration: amplitude 200 μV, duration 1 sec. Time of presentation of flash marked by dot [sic] below trace.

In the preconvulsive phase, as a result of the formation of a GPEE in LGB, considerable enhancement of specific sensory activity was observed in the system of genicular efferent connections. This led to a marked increase in the evoked potential in the corresponding zone of the visual cortex and to the appearance of photogenic compulsive motor responses. In the convulsive phase, as the formation of the GPEE continued, besides the processes mentioned above a disturbance of the general mechanisms of stabilization of brain electrical activity also took place, with a consequent lowering of the threshold of convulsive activity. Against this background, impulses not only from the GPEE in LGB, but also from other brain structures could evoke a generalized paroxysmal after-discharge. Evidence of a disturbance of the normal balance of excitability between the structures responsible for general stabilization of rhythmic brain activity and of the appearance of increased predisposition in the animals to the formation of convulsive responses was given by fluctuations in the level of nonspecific brain activation during the period of the convulsive phase.

The dynamics described above shows that the whole period of formation of the experimental neuropathological syndrome induced by the creation of a GPEE in LGB with the aid of TT can be divided into phases: 1) preconvulsive (the phase of formation of changes in the system of specific visual efferent projections of the corresponding LGB) and 2) convulsive (the phase of functional changes in nonspecific mechanisms of stabilization of electrical activity in different parts of the brain).

As was shown previously [3], local injection of TT into LGB causes a disturbance of synaptic inhibition in that nucleus (the formation of a GPEE). These disturbances, on the one hand, cause a considerable increase in the intensity of the sensory signal in LGB, which determines the specific functional changes in the system of genicular efferent projections. On the other hand, disinhibition of the relay neurons of LGB under the influence of TT and hyperactivity of the resulting GPEE determine the nonspecific functional changes in the system controlling cerebral electrogenesis. Under normal conditions, the function of disinhibition of LGB is known to belong to certain regions of the mesencephalic reticular formation [12]. Consequently, as regards its effect, the specific action of TT on the nucleus can be compared with the extremely enhanced effect of "activating" zones of the mesencephalic reticular formation, depressing the activity of inhibitory interneurons in LGB. A stable increase in activity of the LGB relay neurons can induce, through negative feedback, a response of coupled "depression" of the corresponding activating structures. Such a response, in particular, can be brought about by synchronizing structures, antagonistic in relation to the activating mesencephalic reticular formation, and connected anatomically with LGB [1, 9, 11].

Fluctuations in the level of nonspecific brain activation, especially periods of depression of activity of desynchronizing regions of the mesencephalic reticular formation, are an important factor in increasing the predisposition of animals toward the formation of convulsive responses [5, 13]. Against the background of enhanced epileptic reactivity of the brain, associated with a disturbance of the normal balance of excitation between structures responsible for general stabilization of rhythmic electrical activity, the enhanced volley of excitation which follows from the GPEE in LGB may provoke the formation in the experimental animals of epileptic paroxysms manifested clinically and electrographically. A role can also be postulated for other mechanisms of enhancement of epileptic predisposition of the brain under these conditions (an increase in general excitability, involvement of other synchronizin structures).

The sequence of events examined above may thus be due to pathological enhancement of excitability in neuronal chains responsible, on the one hand, for the conducting of the specific sensory signal through LGB and, on the other hand, for nonspecific control of sensory excitation on its course through the visual relay nucleus when a GPEE is formed in it. Both processes are produced by activity of the GPEE, which leads to the formation of a pathological system with different specific and nonspecific components.

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HEMATOPOIETIC ORGANS OF MICE AFTER A SINGLE INJECTION OF HYDROCORTISONE

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The method of exogenous cloning of hematopoietic stem cells (colony-forming units — CFU) in the spleen and bone marrow of lethally irradiated recipients was used to study the population kinetics and direction of differentiation of CFU from mice receiving a single dose (5 mg per mouse) of hydrocortisone. Against the background of prolonged involution of the lymphoid tissue changes took place in the population and differentiation of CFU. Meanwhile the CFU concentration in the spleen and femoral bone marrow of the mice remained constant. After administration of the hormone, the powers of differentiation of CFU from spleen and bone marrow changed sharply in opposite directions: Marrow CFU behaved like splenic CFU whereas splenic CFU behaved like marrow CFU of normal mice. It is suggested that these effects are due to redistribution of T lymphocytes and not to the direct cytotoxic action of hydrocortisone on the CFU population.

KEY WORDS: hematopoietic organs; hydrocortisone; stem cells; differentiation.

Injection of corticosteroids into animals and man causes incidental involution of the lymphoid organs, with rapid and profound lymphocytopenia. These changes take place chiefly as a result of destruction of immunologically immature, cortisone-sensitive and a redistribution of immunologically competent, cortisone-resistant T lymphocytes [2-5, 11]. It is therefore natural to suggest that steroid hormones have a direct or indirect effect on the pool of hematopoietic stem cells for, on the one hand, stem cells are morphologically equivalent to lymphocytes and, on the other hand, they are closely interconnected with T lymphocytes [1, 6, 9].

The object of this investigation was to study the possible role of hydrocortisone in regulation of the number and differentiation of stem cells taking place during involution of lymphoid tissues.

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