EFFECT OF DIAZEPAM ON EPILEPTIC ACTIVITY IN RATS WITH EXPERIMENTAL PHOTOGENIC EPILEPSY

M. B. Rekhtman, B. A. Konnikov, and G. N. Kryzhanovskii *

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The effect of diazepam (in a dose of 4 mg/kg body weight) on the specific and nonspecific mechanisms of formation of experimental photogenic epilepsy, produced by injection of tetanus toxin into the lateral geniculate body (LGB), and the formation of a generator of pathologically enhanced excitation (GPEE) in that nucleus, was studied in chronic experiments on rats. In the above dose diazepam was found to have a relatively weak action on the degree of pathological enhancement of sensory visual stimuli in LGB in which a GPEE was formed, it facilitated the appearance of focal interictal discharges in LGB, and for 1 h it completely suppressed generalized epileptic activity in the experimental animals.

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

The study of the pathogenesis of experimental photogenic epilepsy [5], arising after the formation of a generator of pathologically enhanced excitation (GPEE) in the lateral geniculate body (LGB) [4] as a result of local injection of tetanus toxin (TT) into that nucleus, has shown that the formation of this syndrome is based on two main pathogenetic factors: 1) pathological enhancement of specific sensory excitation as it passes through the thalamic relay nucleus; 2) disturbance of the nonspecific mechanisms of stabilization of rhythmic brain electrical activity. The object of the present investigation was to determine the effect of diazepam — one of the most active antiepileptic agents — on specific and nonspecific pathogenetic mechanisms of epileptogenesis in rats with experimental photogenic epilepsy.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 250-300 g. Photogenic epilepsy was induced in the animals by the formation of a GPEE in LGB. For this purpose TT (specific toxicity $5 \cdot 10^5$ mouse MLD/ml) was injected stereotaxically in a volume of $0.2 \cdot 10^{-4}$ ml into LGB. Subcortical (glass-insulated nichrome wire, 100 μ in diameter) and cortical (silver ball) electrodes were implanted chronically into LGB, the visual cortex (VC) and sensomotor cortex of both hemispheres respectively. A monopolar recording technique was used: The reference electrode was located on the boundary between the frontal and temporal lobes. Muscular activity was recorded by a bipolar electrode from the extensor muscles of the animal's hind limb. Throughout the experiment the rats lay in a special hammock, causing minimal restraint. In the various phases of photogenic epilepsy the animals were given intramuscular injections of diazepam (from Gedeon Richter, Hungary) in a dose of 4 mg/kg body weight and the dynamics of its action was studied. After the experiments the region of injection of TT and location of the subcortical electrodes were verified morphologically.

EXPERIMENTAL RESULTS

Characteristic features of pathologically increased photoreactivity appeared in the animals, 5-7 h after local injection of TT into LGB, in the thalamocortical projection system on the site of injection of TT [3, 5]. One such feature was a marked increase in the primary evoked potential in the ipsilateral VC. Analysis of associated changes in evoked activity in LGB (after injection of TT into it) and the ipsilateral VC showed that the changes observed in reactivity in VC were due to pathological enhancement of specific sensory excitation in LGB as a result of the formation of a GPEE in it [3]. Besides the above-mentioned changes in photoreactivity in the projection region of VC, 10-12 h after injection of TT into LGB the animals developed characteristic

*Corresponding member, Academy of Medical Sciences of the USSR.

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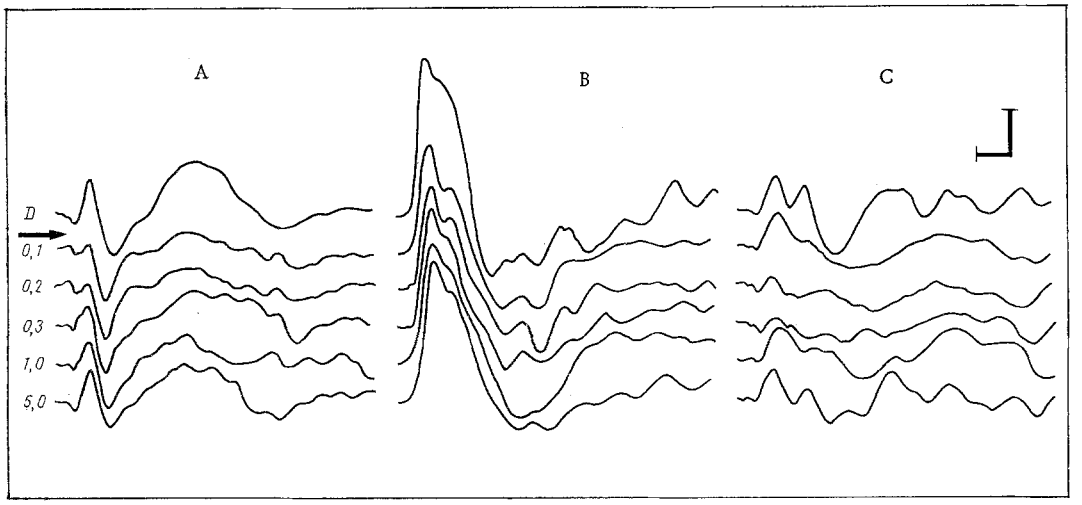

Fig. 1. Effect of diazepam on evoked potentials in VC of rats. A) Control (intact animal); B and C) 14 h after injection of TT into LGB; B) ipsi-, C) contralateral side. Evoked responses: above arrow before, below arrow after injection of diazepam. Numbers indicate time (in h) after injection of diazepam. Each record obtained by computer averaging of 40 evoked potentials. Calibration: amplitude 100 μV, time 50 msec.

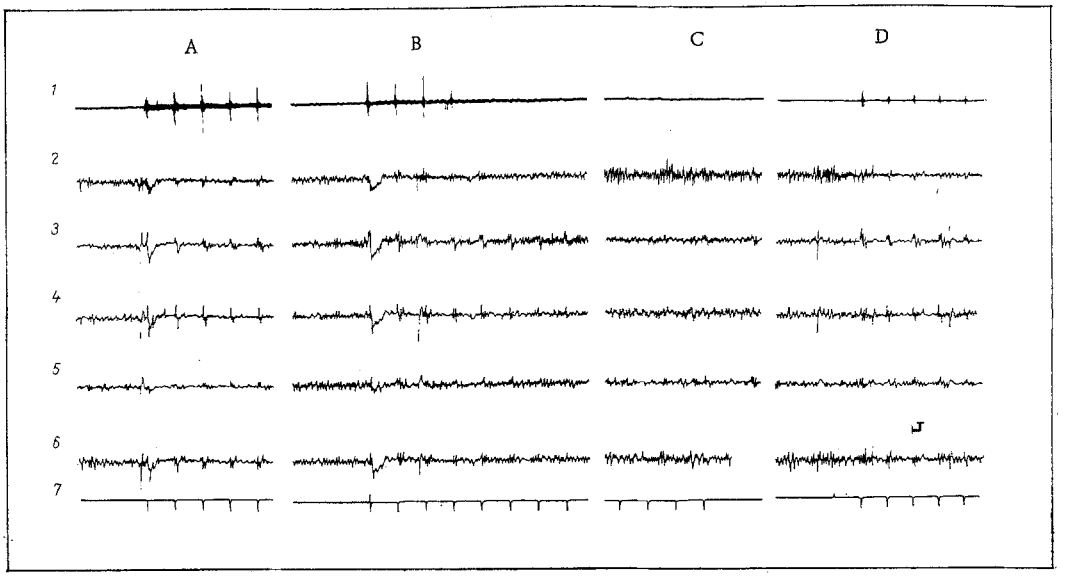

Fig. 2. Effect of diazepam on compulsive motor responses. Recording made 14 h after injection of TT into right LGB. A) Compulsive movements before injection of diazepam; B) 1 min, C) 12 min, D) 65 min after injection of diazepam. 1) Myogram of extensor of hind limb; 2) sensomotor cortex; 3) right LGB; 4) right VC; 5) left LGB; 6) left VC; 7) marker of photic stimulus. Calibration: amplitude 100 μV, time 1 sec.

compulsive movements in response to photic stimulation. These compulsive movements were connected with pathological enhancement of excitation in LGB in the rats, for the ventral part of LGB is a component of the specific visuomotor pathway [7,11,14]. The first epileptic fit occurred in the rats 15-17 h after injection of TT into LGB. Usually the most typical form of paroxysmal activity consisted of primary generalized clonico-tonic convulsions.

A few tens of seconds after injection of diazepam into the intact (control) animals, they developed a characteristic decrease in amplitude of the negative components of the evoked response in VC (see also [1]);

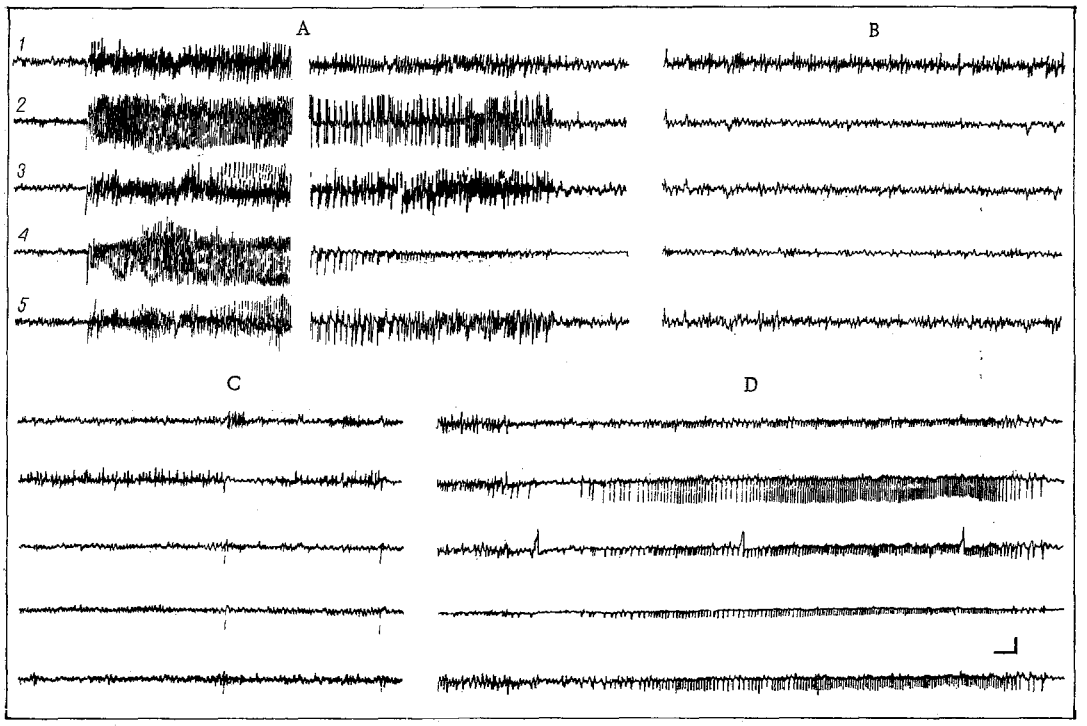

Fig. 3. Effect of diazepam on epileptic activity. Recording made 14.5 h after injection of TT into right LGB. A) Beginning and end of generalized epileptic after-discharge before injection of diazepam; B) 5 min after injection of diazepam; C) interictal discharges in right LGB 12 min after injection of diazepam; D) epileptic after-discharge 70 min after injection of diazepam. 1) Right sensomotor cortex; 2) right LGB; 3) right VC; 4) left LGB; 5) left VC. Calibration: amplitude 200 μV, time 3 sec.

the amplitude of both the primary negative wave and of the slow negative wave was reduced (Fig. 1A). Complete recovery of the shape of the evoked potentials in this case took place 1-5 h after administration of the drug. Injection of diazepam into the experimental animals at different stages of formation of photogenic epilepsy also led to a decrease in amplitude of the extremely augmented negative components of the evoked response in VC ipsilateral to the GPEE in LGB (Fig. 1B). However, the corresponding potential still remained above normal. Under the influence of diazepam a decrease in the voltage of the negative waves of the evoked potentials also was observed in the contralateral VC (Fig. 1C). Restoration of the parameters of the evoked potentials in these cases took 2-5 h. It can tentatively be suggested that the relative decrease in amplitude of the negative components of the evoked potentials in VC of the control and experimental animals was due to the action of diazepam on subcortical [1] and cortical [2, 6] mechanisms of conduction of visual excitation and, to a lesser degree, to depression of the pathologically enhanced excitation in LGB after injection of TT into it and the formation of the GPEE.

As was stated above, before systemic injection of diazepam each photic stimulus could induce shivering, leaping, or jumping in the animals (see the correlation between discharges of muscle activity of the animal's limb and flashes in Fig. 2A). These responses disappeared 1 min after injection of diazepam (Fig. 2B, C) and began to recover only after 1 h had elapsed (Fig. 2D). Since diazepam did not completely suppress the pathologically enhanced visual signal on its way through the corresponding LGB to the ipsilateral VC in the experimental animals, but completely abolished the compulsive movements for several tens of minutes, it can be postulated that depression of these motor responses to photic stimulation was due to the stabilizing effect of diazepam on excitability of the brain-stem centers of visuomotor coordination, connected anatomically with LGB [7, 11, 14].

Epileptic paroxysms proper, manifested both as convulsions and electroencephalographically, were completely suppressed 1-2 min after injection of the above dose of diazepam for 1 h (Fig. 3B).

Usually in the absence of diazepam the onset of hypersynchronized high-amplitude activity in LGB after the formation of a GPEE in it was observed during a period of generalized epileptic after-discharges, and it was evidently the cause of their initiation (Fig. 3A, see also [5]). This was responsible for the absence of

focal interictal discharges in LGB of the animals after local injection of TT into that nucleus. However, 10-20 min after injection of diazepam, a characteristic focal pathological independent rhythm was observed in LGB on the side of the GPEE. Series of high-amplitude spikes, resembling interictal discharges in their course, appeared sporadically in that nucleus (Fig. 3C). These series of spikes in LGB were regularly interrupted by a spontaneous generalized potential, after which they formed again. A gradual increase in amplitude of its component spikes was observed before the end of this interictal discharge (Fig. 3C).

About 1 h after injection of diazepam individual features of photogenic epilepsy began to be restored in the animals. The onset of the first epileptic discharges in this period was linked with the strongest epileptic activity in LGB on the side of the GPEE (Fig. 3D).

The results showed that when a GPEE is formed in LGB and the experimental animals develop a syndrome of photogenic epilepsy, diazepam in the dose mentioned is comparatively ineffective in suppressing the focal epileptic changes in that nucleus. Pathological enhancement of specific sensory excitation in the corresponding LGB, leading to a marked increase in amplitude of the primary evoked potential in the ipsilateral VC, could not be completely abolished by injection of diazepam. Moreover, against the background of depression of the general predisposition of the animals to paroxysmal activity, focal epileptic discharges appeared in the corresponding LGB.

However, very soon after systemic administration of diazepam, the generalized electroencephalographic epileptic paroxysms and the convulsions themselves disappeared.

These facts show that the main target for the antiepileptic action of diazepam is not the activity of the GPEE in LGB, but the state of enhanced predisposition to paroxysmal activity induced by the formation of the GPEE in the thalamic relay nucleus. This ability of diazepam to abolish the predisposition of the brain to generate epileptic discharges has also been demonstrated by experiments with metrazol [8,13], with a model of amygdalar epilepsy [12], and in the clinical treatment of fits of the "petit mal" type [9,10].

However, diazepam is less effective in its action on cortical epileptic foci [12,13]. As the results described above show, it has no significant effect on a GPEE in LGB in animals with photogenic epilepsy. The latest research in the writers' laboratory, on a model of spinal myoclonia has shown that diazepam is relatively ineffective against a GPEE in the spinal cord, although it depresses the accompanying clinical manifestations of the syndrome.

The therapeutic effect of diazepam is therefore connected primarily with temporary stabilization of the nonspecific mechanisms of formation of the rhythmic electrical activity of the brain and, to a lesser degree, with depression of the activity of the GPEE in LGB as an epileptic focus.

LITERATURE CITED

1. V. A. Belyakov, L. N. Sinitsyn, T. A. Sabanova, et al., Vengersk. Farmakoter., No. 4, 129 (1976).
2. V. V. Zakusov and R. U. Ostrovskaya, Neirofiziologiya, 3, 582 (1971).
3. B. A. Konnikov, M. B. Rekhtman, and G. N. Kryzhanovskii, Neirofiziologiya, 10, 142 (1978).
4. G. N. Kryzhanovskii, Zh. Nevropatol. Psikhiat., No. 11, 1730 (1976).
5. G. N. Kryzhanovskii, M. B. Rekhtman, B. A. Konnikov, et al., Byull. Éksp. Biol. Med., No. 1, 22 (1976).
6. R. U. Ostrovskaya, Farmakol. Toksikol., No. 1, 7 (1972).
7. J. Altman and M. B. Carpenter, J. Comp. Neurol., 116, 157 (1961).
8. M. Deteuchi and E. Costa, Neuropharmacology, 12, 1059 (1973).
9. H. Hershon and M. Parsonage, Lancet, 2, 859 (1969).
10. H. Gastaut et al., Rev. Neurol., 112, 99 (1965).
11. S. Polyak, The Vertebrate Visual System, Chicago (1957), pp. 288-389.
12. R. Racine et al., Electroenceph. Clin. Neurophysiol., 38, 355 (1975).
13. R. Spahlmann and B. Colley, Neurology (Minneapolis), 17, 281 (1967).
14. P. D. Wall et al., Electroenceph. Clin. Neurophysiol., 5, 385 (1953).