# PHARMACOLOGICAL ANALYSIS OF THE MECHANISM OF MYOCLONIC CONVULSIONS IN RATS

Z. A. Zorina and D. A. Fless

UDC 616.74-009.24-092.9:615

Injection of central stimulants with action directed toward the hippocampus or neocortex showed that substances stimulating the hippocampus (bemegride) cause the development of myoclonic convulsions whereas drugs with action of a different character (caffeine and amphetamine) give rise to convulsions and hyperkinesias of other types.

It is suggested that the similarity between the external manifestations of myoclonic convulsions produced by different factors is due to the role of the limbic system in their genesis.

* * *

Several types of clonic convulsions differing in their central mechanism and external manifestation are observed in the audiogenic epileptiform response of rats. Convulsions of myoclonic type differ from others in the frequency and amplitude of the contractions, and also in the strictly definite sequence of their spread: from the facial muscles to the muscles of the neck and then to the forelimbs and hind limbs [7]. The excitation producing them is primarily formed, it seems, in the subcortical auditory nuclei [4, 8], and the efferent component is the cortex, because other types of clonic convulsions may appear without cortical participation [5]. Myoclonic convulsions can be produced in different ways. In response to the action of an acoustic epileptogenic stimulus they may develop after repeated applications. They also constitute the first, and if small doses are used, the only convulsive phase of the leptazol convulsion [4] and are observed during stimulation of the hippocampus, the septum, and the temporal cortex [11]. Experiments involving stimulation of the hippocampus or blocking of its function, together with results indicating the excitatory action of leptazol on the limbic system [1, 2, 16, 17] have led to the conclusion that the limbic system plays an important role in the genesis of myoclonic convulsions [11].

The object of the present investigation was to test this hypothesis by comparing the type of convulsion developing after administration of large doses of central stimulants differing in their effect on the convulsive threshold of the hippocampus: bemegride, caffeine, and amphetamine.

TABLE 1. Development of Different Types of Convulsions after Administration of Pharmacological Agents

| Drug | Dose (in mg/kg) | Mode of injection | Number of experiments | Myoclonic convulsion (%) | Clonic convulsions (%) | Absence of convulsions (%) |
|---|---|---|---|---|---|---|
| Bemegride | 10 | Subcutaneously | 5 | 60 | – | 40 |
| " | 15-25 | " | 10 | 100 | – | – |
| " | 40-60 | " | 10 | 100 | 100 | – |
| Caffeine | 200-5000 | " | 15 | – | 7 | 93 |
| " | 750 | Intraperitoneally | 10 | – | 70 | 30 |
| Amphetamine | 10, 25, 60 | " | 15 | – | – | 100 |

Laboratory of Pathophysiology of Higher Nervous Activity, Department of Physiology of Higher Nervous Activity, Faculty of Biology and Soil Science, Moscow University (Presented by Academician V. V. Parin). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 67, No. 1, pp. 48-50, January, 1969. Original article submitted August 19, 1967.

## EXPERIMENTAL METHOD

Rats of line KM weighing 250-300 g were used in the experiments. Bemegride and caffeine were injected subcutaneously, amphetamine and, sometimes, caffeine intraperitoneally. Observed changes in behavior and the character of the convulsions were fully described and recorded. The doses of the drugs were increased from experiment to experiment until myoclonic convulsions appeared or until the development of toxic manifestations, leading to death of the animal.

## EXPERIMENTAL RESULTS AND DISCUSSION

Injection of Bemegride. Injection of leptazol and bemegride into unanesthetized rabbits immobilized by the curariform agent diplacin lowers the convulsive threshold of the motor cortex and hippocampus, the effect being much more marked in the latter and accompanied by EEG-activation and by spontaneous paroxysmal discharges. In the present experiments, bemegride, a substance related to leptazol but more active and more toxic [9], produced single spasms of the eyelids, ears, and vibrissa in 60% of animals when given in a dose of 10 mg/kg. In doses of 15, 20, and 25 mg/kg, bemegride always produced typical myoclonic convulsions only, and not until the dose was increased to 40-60 mg/kg was the myoclonus followed by a clonicotonic fit (Table 1).

Injection of Caffeine. In a dose of 25 mg/kg caffeine considerably lowered the convulsive threshold of the neocortex (by 2-2.5 times) and increased the duration of the after-discharges for 1.5-2 h. The threshold of the hippocampus remained unchanged or was slightly increased [1, 2, 17]. Transection of the brain at various levels did not modify the effect of caffeine administration [3], indicating that caffeine stimulates the cortex directly. In the present experiments subcutaneous injection of caffeine in a dose of 200 mg/kg caused severe disturbances of respiration and of movement coordination, leading to lacrimation and tremor, while if the dose was increased, it caused death of the animal. After intraperitoneal injection of caffeine in a dose of 750 mg/kg, 70% of the animals developed clonicotonic convulsions. No myoclonic convulsions were observed in any animal. Excitation of the neocortex produced by caffeine or electrical stimulation of its motor area [11] is thus insufficient to cause the development of myoclonic convulsions. Probably the development of such convulsions after injection of leptazol and bemegride must properly be attributed to excitation of the hippocampus.

Injection of Amphetamine. In a dose of 5 mg/kg it had no significant effect on the convulsive threshold of the hippocampus, while the threshold of appearance of after-discharges may be elevated by 30% [1, 10].

In the present experiments when amphetamine was injected in doses of 10, 25, and 60 mg/kg, the development of an "amphetamine stereotype" [12] was observed, its intensity increasing with an increase in the dose. Myoclonic convulsions did not develop after injection of amphetamine even when a lethal dose (60 mg/kg) was used.

The results indicate that for convulsions of myoclonic type to develop following administration of pharmacological agents, just as for the development of audiogenic myoclonus [11], excitation of limbic structures is essential. Consequently, the central mechanisms of myoclonic convulsions produced by various epileptogenic factors evidently possess more in common than simply their efferent components (the motor cortex and pyramidal tract), as has hitherto been considered [5], for they also share the excitation of certain other structures, notably the limbic system, and also subcortical levels of the auditory analyzer, excited not only during audiogenic myoclonus [4, 8], but also during the action of leptazol [18] and during electrical stimulation of the hippocampus [15].

Since the picture of myoclonic convulsions can be fully reproduced only by stimulation of the hippocampus and certain other limbic structures (stimulation of the medial geniculate body and motor cortex causes development of convulsions of a totally different type), it is postulated that the type of paroxysmal activity which determined the external character of manifestation of the convulsion is in fact formed in the structures of the limbic system. This hypothesis corresponds to data indicating participation of the amygdalo-hippocampal system in the spread and intensification of paroxysmal activity regardless of where it arises [13-15].

Hence, the similar outward expression of convulsions of myoclonic type produced by different methods (acoustic, electrical, or pharmacological stimulation) can be explained by participation of the hippocampus and, possibly, other structures of the limbic system in each case. It is at the level of the limbic system that excitation arriving from different primary foci is integrated and from which it spreads to the motor cortex, the common efferent component for convulsion of this type.

## LITERATURE CITED


1. L. Kh. Allikmets, Experimental and Clinical Basis of the Use of Neurotropic Agents [in Russian], Leningrad (1963), p. 6.
2. L. Kh. Allikmets and Yu. S. Borodkin, Farmakol. i Toksikol., No. 6, 647 (1964).
3. Yu. S. Borodkin, Farmakol. i Toksikol., No. 5, 515 (1964).
4. K. G. Gusel'nikova, Nauchn. Dokl. Vyssh. Shkoly. Biol. Nauki, No. 1, 69 (1959).
5. B. I. Kotlyar, Nauchn. Dokl. Vyssh. Shkoly. Biol. Nauki, No. 2, 73 (1959).
6. B. I. Kotlyar and D. A. Fless, Nauchn. Dokl. Vyssh. Shkoly. Biol. Nauki, No. 2, 98 (1962).
7. L. V. Krushinskii and L. N. Molodkina, Zh. Vyssh. Nervn. Deyat., No. 5, 780 (1960).
8. A. F. Semiokhina, Zh. Vyssh. Nervn. Deyat., No. 2, 278 (1958).
9. V. A. Fateev, Farmakol. i Toksikol., No. 6, 662 (1964).
10. L. P. Fedyaeva, in: Proceedings of a Scientific Conference on the Physiology and Pathology of Cortico-Visceral Interrelationships and Functional Systems of the Organism [in Russian], Vol. 2, Ivanovo (1965), p. 396.
11. D. A. Fless and Z. A. Zorina, Byul. Éksperim. Biol. i Med., No. 10, 43 (1965).
12. E. L. Shchelkunov, Farmakol. i Toksikol., No. 5, 628 (1964).
13. F. Angeleri, G. Faleg, and S. Parigi, Riv. Neurobiol., 4, 241 (1958).
14. F. Angeleri, F. Ferro-Milone, and S. Parigi, Electroenceph. Clin. Neurophysiol., 16, 100 (1964).
15. R. Elul, Electroenceph. Clin. Neurophysiol., 16, 470 (1964).
16. M. Kletzkin, Ann. N. Y. Acad. Sci., 96, 263 (1962).
17. M. Monnier and P. Krupp, Arch. Internat. Pharmacodyn., 127, 337 (1960).
18. F. E. Starzl, W. T. Niemer, M. B. Dell, et al., J. Neuropath. Exp. Neurol., 12, 262 (1953).