A STUDY OF THE ROLE OF VARIOUS DIVISIONS OF THE CENTRAL NERVOUS SYSTEM IN THE MECHANISM OF THE CONVULSIVE ACTION OF METRAZOL

R. Yu. Il'yuchenok and R. U. Ostrovskaya

Laboratory of Pharmacology (Head, Candidate of Medical Sciences R. Yu. Il'yuchenok), Institute of Experimental Biology and Medicine (Director, Professor E. N. Meshalkin) of the AN SSSR, Novosibirsk
(Presented by Active Member AMN SSSR V. V. Zakusov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 55, No. 3, pp. 55-60, March 1963
Original article submitted March 20, 1962

Metrazol possesses marked convulsive activity, for which reason it is used for the pharmacological evaluation of the efficacy of anticonvulsant drugs [6, 13, 17, 18, 19]. In addition, the preparation is widely used for the activation of epileptic attacks in order to facilitate the diagnosis during a quiescent period, especially in cases of focal cortical fits [14, 16, 21, 24, 25]. The awakening action of metrazole is also well known [1, 8, 9, 15, 22, 27].

Schoen [26] carried out experiments with "thalamic" and decerebrate animals, and also with animals in which a section was made between the medulla and the spinal cord, from which he concluded that the action of metrazol was associated with its effect on all the divisions of the central nervous system, although, according to his findings, doses causing convulsions in animals in which the brain was divided between the anterior and posterior colliculi were from 3 to 4 times larger than the doses possessing a convulsant action in "thalamic" animals. It has been found [5] that metrazol affects the summation of impulses in the central nervous system more strongly than during the reflex transmission of excitation, and shortens the motor chronaxie to a much greater degree than do analeptics acting on the spinal cord. This is regarded as proof that the drug acts mainly on the mid-brain, although the role of the thalamus in the mechanism of action of metrazol is admitted. According to a number of workers [10], the convulsive action of metrazol is not exhibited on structures lying below the diencephalon. Hence, despite the wide application of metrazol in both clinical practice and experimental research, the question of the central structures concerned in the convulsive action of the drug remains largely unsolved.

In order to compare the electrographic and clinical manifestations of the convulsive attack after exclusion of various regions of the brain, we studied the convulsant action of metrazol in animals in which the brain stem had been divided at different levels.

EXPERIMENTAL METHOD

The electrical activity of the brain was investigated in experiments on 90 cats and rabbits; the potentials were picked up by means of steel needles inserted into the bone in areas corresponding to the projections of the sensomotor and optic areas of the cortex, and recorded by means of an eight-channel ink-writing electroencephalograph manufactured by the firm of Kaiser.

Experiments were carried out on animals with an intact brain and on animals in which the brain stem was divided: between the 1st and 2nd cervical vertebrae (Bremer's encephale isole) [11, 12], in the region of the nuclei of the trigeminal nerve (trigeminal section); between the anterior and posterior colliculi (Bremer's cerveau isole); along a place passing anteriorly to the anterior colliculi and emerging on the base of the brain posteriorly to the mamillary bodies (premesencephalic section). The sections were carried out either mechanically or electrolytically. The technique of section has been divided in greater detail previously [7]. The drug under study – pentamethylenetetrazol (metrazol) – was injected intravenously, into the carotid artery, or into the cerebral ventricles.

EXPERIMENTAL RESULTS

The injection of metrazol caused characteristic changes in the electrical activity of the brain. Initially, a low-amplitude, high-frequency activity was observed, which changed when the dose was adequate (10-20 mg/kg or more)

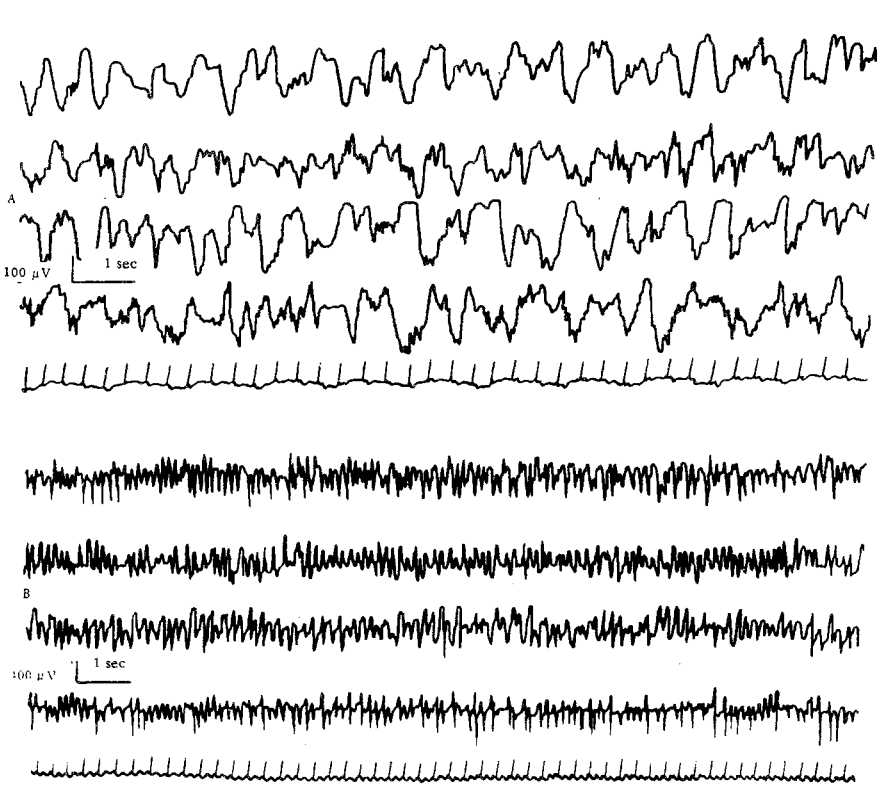

Fig. 1. Effect of metrazol on the EEG of a cat with "cerveau isolé" following brain section. Significance of the curves (from above down): EEG of the left sensomotor and optic regions, and of the right sensomotor and optic regions of the cerebral cortex; ECG: A) before injection; B) 2 min after injection of 20 mg/kg metrazol intravenously.

quickly into a high-voltage (up to 400-600 μV) series of pointed rhythmic discharges of varied frequency (spikes), following each other in continuous succession. This pattern of convulsive discharges developed synchronously in both hemispheres. Immediately after the convulsive discharges followed a period of depression, characterized by the complete absence of electrical activity. At the end of this period sporadic, pointed waves appeared, alternating with slow, high waves, after which developed another period of high-voltage spikes, alternating with depression of the electrical activity in all parts of both hemispheres.

The pattern described above was observed in animals with an intact brain after injection of metrazol intravenously in a dose of 10-20 mg/kg, or into the carotid artery in a dose of 3-5 mg; closely similar doses were required to give the picture of a convulsive discharge on the EEG when injected intraventricularly. With a further increase in the size of the dose, the period of the convulsive discharges on the EEG became more prolonged. The appearance of the convulsive discharges on the EEG was accompanied in the animals by clonic-tonic spasms of the muscles of the trunk, head, and extremities.

After section of the brain of the "encéphale isolé" type, metrazol also caused an electroencephalographic pattern of a convulsive fit; it appeared after the same dose of the drug as in the animals with an intact brain. Under these circumstances convulsive spasms were observed only in the head muscles, developing synchronously with the convulsive discharges on the EEG; the trunk muscles remained immobile at this time. Only when the dose of metrazol was increased to 150-170 mg/kg were very slight spasms of the muscles of the trunk and limbs observed, not synchronous with the convulsive discharges on the EEG, but the obvious pattern of the convulsive fit characteristic of the animals with an intact spinal cord did not develop. Convulsive discharges could also be observed in animals with a trigeminal section of the brain stem and a "cerveau isolé" (Fig. 1), but the dose of the drug causing the effect had to be increased slightly (20-25 mg/kg intravenously). Even when as a result of section the entire mesencephalon was separated from the higher divisions (premesencephalic section), administration of metrazol was followed by the appearance of characteristic convulsive spikes (Fig. 2). In this case, the production of the electroencephalographic pic-

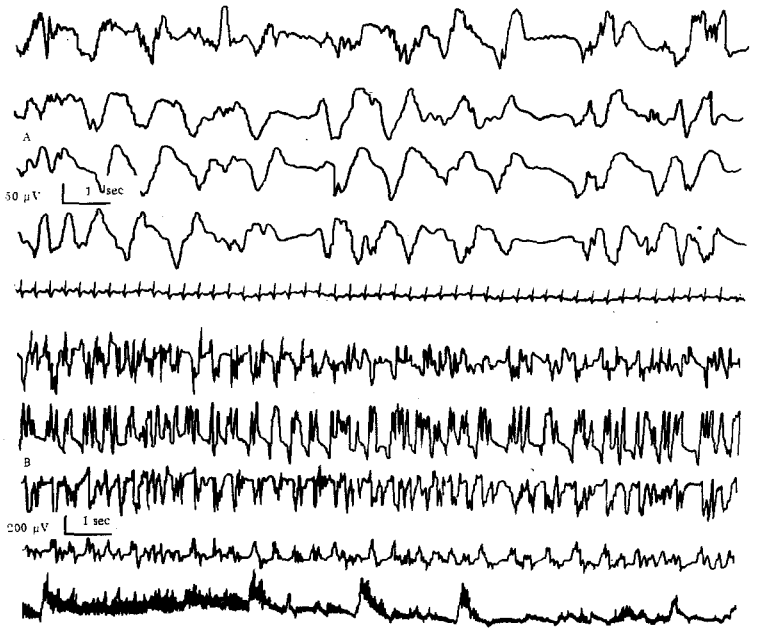

Fig. 2. Effect of metrazol on the EEG of the rabbit after premesencephalic section. Significance of the curves (from above down): EEG of the left sensomotor and optic, and right sensomotor and optic regions of the cerebral cortex; ECG; A) before injection; B) 1 min after injection of 70 mg/kg metrazol intravenously.

ture of a convulsion in animals with premesencephalic section required larger doses than in animals with a more caudal section or with an intact brain; the dose required was 50-100 mg/kg.

After trigeminaland premesencephalic section, and in animals with cerveau isole, the appearance of convulsive discharges on the EEG of the animals was accompanied by the development of spasms of the trunk, limbs, and head, the severity of which increased as the dose injected increased. If in these animals the brain was divided at the cerveau isole level, the spasms of the trunk and limbs disappeared and could no longer be produced even by large doses of metrazol. The muscles of the head continued to contract in the rhythm of the convulsive discharges on the EEG.

The preliminary injection of substances blocking the central cholinergic (amisil, benzacine, in a dose of 0.5 - 2 mg/kg intravenously) or adrenergic (chlorpromazine in a dose of 3-5 mg/kg intravenously) structures did not prevent the convulsant effect of metrazol. However, after a preliminary injection of chlorpromazine the effect of metrazol was rather weaker, and larger doses of the drug were needed in order to produce a clearly defined electroencephalographic and clinical picture of convulsions.

It may be concluded from these experimental results that the spinal cord has no essential role in the mechanism of the convulsant effect of metrazol, which is in agreement with the data given in the literature [2, 3, 4, 20, 23, 26]. The presence of convulsions of the head muscles synchronized with the convulsive discharges on the EEG after division of the brain to give "encéphale isolé" may probably be explained by preservation of the connections of the facial nerve with its nuclei.

The presence of connections between the spinal cord and the caudal part of the brain stem (trigeminal section) is sufficient to produce a clear picture of the convulsive spasm of the trunk muscles. However, when this convulsion is produced in animals with an intact brain stem, it is evident that the more rostral divisions of the brain also take part, for in intact animals the convulsant effect of metrazol is observed after administration of somewhat smaller doses. It must be pointed out that the electroencephalographic picture of a convulsion is also observed in animals following complete section above the mesencephalon (premesencephalic section).

Hence, the appearance of convulsive discharges in the cerebral cortex after administration of metrazol does not require the presence of connections with the mesencephalon. This fact may indicate that divisions of the brain situated rostrally to the mesencephalon (probably the diencephalon) take part in the mechanism of the convulsant action of metrazol on the EEG. Nevertheless, the considerable increase in the dose of metrazol required in order to produce the convulsant effect after premesencephalic section demonstrates the important role of the brain stem in the mechanism of the convulsant action of this drug.

SUMMARY

EEG and clinical manifestations of convulsive attack, caused by corazole, were compared in animals with intact brain and in those with the brain stem divided at different levels. Under study was the role of diverse sections of the CNS in the convulsive effect of this preparation. As shown in experiments on 90 cats and rabbits, corazole administration caused the appearance of high-voltage peaked rhythmic dishcarges on the EEG, which developed synchronously in both hemispheres. Periods of convulsive discharges alternated with periods of bioelectric activity depression. The picture of convulsive attack on the EEG was accompanied by marked clonicotonic convulsions. In animals with intact brain tissue, these effects were observed after intravenous injection of corazole in a dose of 10-20 mg/kg and 3 mg (into the carotid artery). In animals with l'encephale isole brain section convulsive discharges on the EEG appeared with the administration of the same dose of corazole; as to the external convulsions – they were noted only in the head muscles. Even after increasing the dose up to 150-170 mg/kg only weak individual jerks were observed in the body muscles. In the trigeminal section and cerveau isole brain section the dose of corazol increased to 20-25 mg/kg to obtain an EEG and clinical picture of convulsive attack. Corazole retains its property to provoke convulsions even after complete separation of the mesencephalon (premesencephal section). However, for this purpose even higher doses of the preparation are required (50 to 100 mg/kg).

Preliminary administration of substances, blocking the central adreno- and cholinoreactive structures did not prevent the corazole effect, although after aminazine administration somewhat higher corazole doses were required to achieve a distinct convulsive effect. A conclusion was drawn on the important role of the brain stem in the EEG and clinical manifestations of the corazole convulsive effect. However, in animals with an intact brain section located more rostrally this effect takes place.

LITERATURE CITED

1. S. Ya. Arbuzov, Farmakol i toksikol., 5, 24 (1949).
2. A. V. Val'dman, Farmakol. i toksikol., 6, 6 (1950).
3. A. V. Val'dman, Farmakol. i toksikol., 2, 12 (1956).
4. V. V. Zakusov, Farmakol., 3, 5 (1943).
5. V. V. Zakusov, Pharmacology of the Nervous System [in Russian]. Leningrad, 1953.
6. Z. N. Ivanova, Farmakol. i toksikol., 4, 23 (1949).
7. R. Yu. Il'yuchenok and M. D. Mashkovskii, Farmakol. i toksikol., 4, 403 (1961).
8. A. N. Kudrin, Fiziol. zh. SSSR, 1, 65 (1954).
9. N. G. Stroikova. In: The Selective Action of Drugs on the Central Nefvous System [in Russian], p. 16, Leningrad, 1958.
10. C. Ajmone-Marsan and F. Marossero, Electroenceph. clin. Neurophysiol., 1950, v. 2, p. 133.
11. F. Bremer, C. R. Soc. Biol., 1935, v. 118, p. 1235.
12. F. Bremer, C. R. Soc. Biol., 1936, v. 122, p. 460.
13. G. Chen, C. Ensor, and R. Portman, Arch. int. Pharmacodyn., 1956, v. 104, p. 333.
14. C. Cure, T. Rasmussen, and H. Jasper, Arch. Neurol. Psychiat, 1948, v. 59, p. 691.
15. W. Driesen, F. Hahn, and W. Rummel, Arch. exp. Path. Pharmak., 1951, Bd. 212, S. 243.
16. H. Gastaut and J. Hunter, Electroenceph. clin. Neurophysiol., 1950, v. 2, p. 263.
17. L. S. Goodman, J. E. P. Toman, and E. A. Swinyard, Am. J. Med., 1946, v. 1, p. 213.
18. L. S. Goodman, E. A. Swinyard, W. C. Brown, et al., J. Pharmacol. exp. Ther., 1953, v. 108, p. 428.
19. L. S. Goodman and A. Gilman, The Pharmacological Basis of Therapeutics, New York, 1955, p. 11, 178, 206.
20. F. Hahn, Arch. exp. Path. Pharmak., 1943, Bd. 202, S. 165.
21. I. C. Kaufman, C. Marshall, A. E. Walker, J. K. Merlis, et al.
22. L. Kirstein, Electroenceph. clin. Neurophysiol., 1952, v. 4, p. 73.
23. V. G. Longo, B. Silvestrini, and D. Bovet, J. Pharmacol. exp. Ther., 1959, v. 126, p. 41.
24. J. K. Merlis, G. Henriksen, and Ch. Grossman, Elecroenceph. clin. Neurophysiol., 1950, v. 2, p. 17.

25. W. Penfield and H. Jasper, Epilepsy and the Functional Anatomy of the Human Brain [Russian translation]. Moscow, 1958.
26. R. Schoen, Arch. exp. Path. Pharmak., 1926, Bd. 113, S. 257.
27. K. Shimizu, S. Refsum, and F. A. Gibbs, Electroenceph. clin. Neurophysiol., 1952, v. 4, p. 141.