ANTIALLERGIC EFFECT OF ETHIMIZOLE

G. R. Broun and A. E. Perel'man

UDC 615.214.3.017:615.218.3

Therapeutic doses of ethimizole increase the number of active neurons in the supramammillary and mammillary regions of the hypothalamus in rabbits infected with Mycobacterium tuberculosis and decrease the intensity of tuberculin allergy in albino mice vaccinated with BCG.

The hypothesis of the functional unity of the hypothalamo-hypophyseal system is confirmed by many experimental observations that procedures influencing the hypothalamus produce regular morphological and functional changes in the endocrine system [10, 15]. The search for pharmacological agents which, by their action on hypothalamic structures, would give a therapeutic effect characteristic of hormones, is therefore perfectly rational. In particular, properties of this type are possessed by ethimizole, a compound belonging to the antiffeines group, synthesized in the Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR [1]. Nontoxic doses of ethimizole, producing excitation of hypothalamic neurons, have been shown to stimulate production of ACTH by the anterior lobe of the pituitary [7].

The antiallergic effect of ethimizole following infection with Mycobacterium tuberculosis or BCG vaccination, i.e., during infection accompanied by hypersensitivity of the delayed type, was studied in the present investigation. As the first step the effect of ethimizole was studied on function of posterior hypothalamic structures in rabbits infected with tuberculosis, and the next step was to study the antiallergic action of ethimizole on albino mice immunized with BCG.

EXPERIMENTAL METHOD

The functional state of the posterior hypothalamus was studied in acute experiments on 13 rabbits weighing 3-3.5 kg; nine rabbits were used in the experiment on the 11-th-16th day after intravenous injection of a virulent culture of M. tuberculosis (strain No. 109) in a dose of 0.15 mg, five of the rabbits receiving ethimizole intravenously before the experiment in a dose of 10 mg/kg; four rabbits were left intact and used as an additional control.

Spike activity of groups of neurons was studied in all the rabbits by Ugolev's method [3] by means of tungsten microelectrodes (diameter of tip 4-10 μ), using extracellular recording. The electrophysiological apparatus, built at the experimental workshops of the Institute of Experimental Medicine, included a cathode follower. Unit activity was recorded on photographic film from a CRO screen.

The electrode was inserted in accordance with the coordinates of Fifkova and Marsala into the posterior hypothalamic nucleus. Next, by means of a micromanipulator with steps of 60 μ, the electrode was passed along a track 3000μ in length. Every step of 60μ, the presence or absence of spike activity was noted.

In the subsequent analysis of the data the electrode track was conventionally divided into five zones, each of 600 μ (Fig. 1). Zone 1 corresponded to the posterior hypothalamic nucleus, zones 2 and 3 to the

Leningrad Research Institute of Tuberculosis. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 70, No. 10, pp. 60-63, October, 1970. Original article submitted March 4, 1970.

TABLE 1. Effect of Ethimizole on Intensity of Tuberculin Allergy in Albino Mice Immunized with BCG (M ± m)

Nature of experiments	Magnitude of tuberculin reaction (in hundredths of a millimeter)	P
Ethimizole (1 course)	25 ± 2.3	< 0.05
" (2 course)	21 ± 2.0	< 0.01
Control.	32 ± 2.6	–

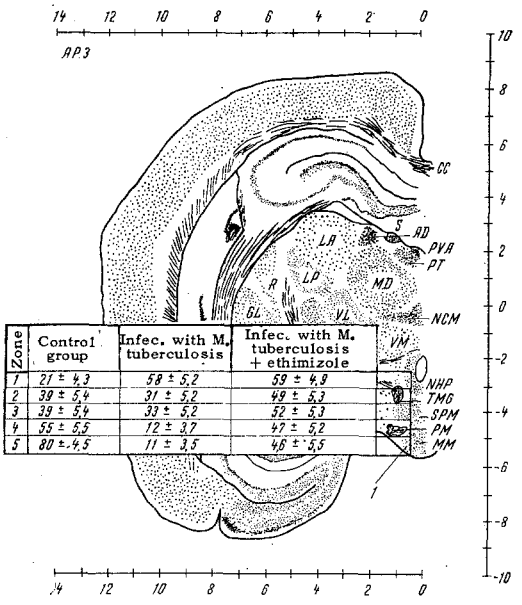

Fig. 1. Frontal plane A P. 3 from atlas of rabbit's brain by Fifkova and Marsala. Electrode track (1), its division into 600-μ zones, and functional state of each zone in animals of different groups are shown.

supramammillary region, and zones 4 and 5 to the region of the mammillary bodies. The percentage of active points was calculated in each 600-μ zone, and this was used as a measure of the functional state of each zone. Corresponding figures for experimental and control groups were compared and the location of the electrode in the hypothalamus was determined by neuromorphological control examination.

The effect of ethimizole on tuberculin allergy was studied in 86 albino mice immunized subcutaneously with 0.06 mg BCG vaccine. Daily for 10 days (from the 30th to the 40th day after immunization) 30 of these mice received ethimizole in a dose of 20 mg/kg, another 30 mice received two of these 10-day courses of the compound (from the first to the 10th and from the 20th to the 30th days after immunization), and the remaining 26 mice were left as the control. The tuberculin test was performed on all animals (40th day after vaccination).

Tuberculin (1:10) was injected in a dose of 0.1 ml by Gray's method [11] into the skin of the plantar surface of the animal's right foot. The same volume of physiological saline was injected into the left foot. The tuberculin reaction was read quantitatively by the writers' own method. A type MK-0-25 mm micrometer was used for this purpose. The plantar surface of the animal's foot in its middle third was placed on the stationary platform of the micrometer. The rotor of the instrument was turned until its uniform rotation operated the ratchet, so that the thickness of the foot could be measured in the selected region. Each foot was measured three times. The difference between the mean measurements of the right and left foot, expressed in hundredths of a millimeter, gave a quantitative assessment for the reaction of each animal to tuberculin. The results of the measurements were analyzed by Student's method and the significance of differences between the control and experiment determined.

RESULTS

The results of experiments to study the functional state of the posterior hypothalamic structures are shown in Fig. 1. In the region of the posterior hypothalamic nucleus (zone 1), a significant increase in the percentage of active points was observed in the infected rabbits compared with the intact control. In zones 2 and 3 (supramammillary region) there was no significant difference, whereas in zones 4 and 5 (mammillary bodies) of the infected rabbits there was a definite decrease in the percentage of active points. These results agree with those published earlier [2]. On the basis of published data concerning the relationship of the mammillary region to regulation of ACTH secretion [9, 10, 12-14], the observed changes can be assessed provisionally as a manifestation of inhibition of the hypothalamic mechanisms of stimulation of ACTH secretion in tuberculosis. This suggestion is in agreement with the many data indicating depression of the function of the pituitary–adrenal cortex system in this disease [4-6, 8].

In rabbits receiving ethimizole, a definite increase in the percentage of active points was found in the supramammillary and mammillary regions compared with infected animals not receiving the compound. The experimental results thus indicate an excitatory effect of ethimizole on posterior hypothalamic neurons, in agreement with the observations of Ryzhenkov [7], who demonstrated the stimulant action of the compound on the pituitary–adrenal cortex system.

The results of experiments to study the effect of ethimizole on tuberculin allergy are given in Table 1. They show that ethimizole, in therapeutic doses, caused a statistically significant decrease in the intensity of the tuberculin reaction in albino mice. This depression of tuberculin allergy was rather more marked in animals receiving two 10-day courses of ethimizole.

Ethimizole, by its action on the hypothalamus, thus causes a significant depression of hypersensitivity of delayed type, which may prove useful when the compound is used clinically.

LITERATURE CITED

1. S. V. Anichkov, N. V. Khromov-Borisov, Yu. S. Borodkin, et al., in: Pharmacology of New Sedatives and Their Clinical Application [in Russian], Leningrad (1962), p. 151.
2. G. R. Broun, Byull. Éksperim. Biol. i Med., No. 2, 40 (1969).
3. V. A. Zabolotnykh, Electrophysiological Investigation of the Hypothalamic Division of the Food Center, Author's Abstract of Candidate's Dissertation, Leningrad (1964).
4. I. N. Komarova, Probl. Éndokrinol., No. 1, 88 (1960).
5. V. S. Libenson, Probl. Tuberk., No. 1, 41 (1960).
6. L. M. Model', Outlines of Clinical Pathophysiology of Tuberculosis [in Russian], Moscow (1962).
7. V. E. Ryzhenkov, Action of Central Neurotropic Drugs on the Pituitary–Adrenal Cortex System in Its Various States, Author's Abstract of Doctoral Dissertation, Leningrad (1968).
8. N. A. Shmelev, in: The Use of Steroid Hormones for Clinical Treatment of Internal Diseases [in Russian], Moscow (1962), p. 119.
9. I. A. Éskin and N. V. Mikhailov, Probl. Éndokrinol., No. 2, 63 (1968).
10. J. Szentogothai, B. Flerko, B. Mess, et al., Hypothalamic Regulation of the Anterior Pituitary [in Russian], Budapest (1965).
11. D. F. Gray and P. A. Jennings, Am. Rev. Tuberc., 72, 171 (1955).
12. J. de Groot and G. W. Harris, J. Physiol. (London), 111, 335 (1950).
13. R. W. Porter, Am. J. Physiol., 169, 629 (1952).
14. R. W. Porter, Am. J. Physiol., 172, 515 (1953).
15. V. Schreiber, The Hypothalamo-Hypophyseal System, Prague (1963).