LITERATURE CITED

1. M. D. Grozdova, Yu. A. Grigorovich, A. M. Zubovskaya, et al., Vopr. Med. Khim., No. 3, 415 (1980).
2. G. I. Dorofeev, L. A. Kozhemyakin, and V. T. Ivashkin, Cyclic Nucleotides and Adaptation of the Organism [in Russian], Leningrad (1978).
3. V. F. Makeeva, G. S. Komolova, I. A. Egorov, et al., Vopr. Med. Khim., No. 1, 59 (1981).
4. N. N. Mayanskaya and L. E. Panin, Usp. Sovrem. Biol., 92, No. 1, 64 (1981).
5. F. Z. Meerson and V. K. Vasil'ev, Byull. Éksp. Biol. Med., No. 9, 297 (1981).
6. F. Z. Meerson, V. E. Kagan, Yu. V. Arkhipenko, et al., Kardiologiya, No. 12, 55 (1981).
7. K. V. Sudakov, Vestn. Akad. Med. Nauk SSSR, No. 9, 10 (1981).
8. K. V. Sudakov and L. S. Ul'yaninskii, Vestn. Akad. Med. Nauk SSSR, No. 11, 37 (1980).

EFFECT OF NICOTINIC AND MUSCARINIC CHOLINOLYTICS ON EXPERIMENTAL EPILEPTOGENESIS

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Among the available antiepileptic agents used in clinical practice there are virtually none able to modify specifically the character of transmission of nervous impulses in brain synapses, although formation of a stable pathological state in epilepsy [3] evidently cannot take place without the participation of various mediator systems, including the cholinergic system.

In connection with the quest for new anticonvulsants, the writers have studied the effect of the nicotinic cholinolytic eterophen (IÉM-506, USSR origin) and the muscarinic cholinolytic metamizil (methyldiazine) [11, 12]. Eterophen, injected intravenously into rabbits, was shown to reduce excitability of the dorsal hippocampus, amygdala, caudate nucleus, and cerebral cortex but to have no effect or to increase only slightly the excitability of the mesencephalic reticular formation. Metamizil, on the other hand, has marked ability to block structures of the ascending reticular activating system (ARAS) and, at the same time, to increase the excitability of the hippocampus and amygdala.

Investigations on a penicillin model of epilepsy [7] have shown that nicotinic cholinolytics eterophen and gangleron,* when administered systemically against the background of epileptiform activity, completely suppressed or reduced the number of seizures in animals, whereas the muscarinic cholinolytic metamizil, on the contrary, provoked the appearance of seizures.

In the present investigation, by using a similar model of penicillin epilepsy, a more detailed study was made of the effect of the above-mentioned drugs and, in particular, of eterophen on epileptogenesis, both before and after the formation of the epileptogenic focus.

EXPERIMENTAL METHOD

Experiments were carried out on 16 male rabbits weighing 3-3.5 kg with chronically implanted electrodes in the dorsal region of the hippocampus, the mesencephalic reticular formation, and the sensomotor cortex. Epileptogenic foci were created by injection of 250 Units

*1,2-Dimethyl-3-diethylaminopropyl-p-isobutoxybenzoate hydrochloride.

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of a solution of the sodium salt of benzylpenicillin in a volume of 1 µl through a chemical electrode [13] introduced into the dorsal hippocampus (areas CA-1 and CA-2).

Eterophen was given in doses of 5 and 10 mg/kg, metamizil in a dose of 1 mg/kg, and gangleron in a dose of 3 mg/kg intravenously; phenytoin sodium was injected intraperitoneally in a dose of 50 mg/kg. Solutions of the latter were made up in 0.1 N NaOH.

In each experiment the animals remained under observation for 2.5 h. The number of interictal discharges in the focus and the number of seizures were analyzed. These parameters were calculated for 15 consecutive 10-min periods. The number of spikes was counted during 1 min of recording and the number of seizures during 10 min of observation. The experimental results were subjected to statistical analysis [10] ($P = 0.05$, $n = 5$).

The experiments were conducted in accordance with two schemes: 1) The drugs were injected 15-20 min before formation of the epileptogenic focus. In control experiments only penicillin was injected into the focus. Values obtained in the control experiments were taken as 100%; 2) the drugs were injected 30 min after the appearance of epileptiform activity. In this case mean values of the number of interictal epileptiform discharges and seizures counted during the first 30 min of recording were taken as 100%. The locations of the recording and chemical electrodes were verified histologically.

EXPERIMENTAL RESULTS

In response to microinjection of penicillin (250 Units) into the dorsal hippocampus, epileptiform discharges appeared in the EEG of all animals in the form of single or grouped spikes; they were recorded initially in the focus but later in other brain structures. Motor convulsions appeared after irradiation of the epileptiform activity from the focus into other parts of the brain and, in particular, into the cerebral cortex. Convulsions alternated with periods of rest during which interictal discharges were recorded on the EEG of all structures. Changes of this kind were observed for 3-4 h.

The results are presented in the form of graphs in Figs. 1 and 2.

Eterophen and gangleron (15-20 min before microinjection of penicillin) completely prevented the development of motor and electrographic manifestations of epileptiform activity in 55 and 60% of experiments respectively.

In the remaining experiments during the first 30 min after injection of penicillin and against the background of gangleron and eterophen motor convulsions and spikes were completely absent. Later these components of epileptiform activity appeared, but in a greatly weakened form (Fig. 1). This process was more marked in the interval from 60 to 90 min.

Phenytoin sodium, under similar experimental conditions, did not completely prevent the appearance of epileptiform activity, but merely weakened it.

The anticonvulsant activity of gangleron and eterophen was much weaker when they were administered after the formation of a focus of epileptiform activity, for they could inhibit convulsions only for a short time (for 30-50 min), while maintaining reduced spike activity on the EEG. Later convulsions also appeared but their frequency was reduced. Seizure activity was suppressed to a greater degree after administration of eterophen and gangleron than of phenytoin sodium (Fig. 2).

By contrast with nicotinic cholinolytics, metamizil definitely potentiated seizure activity. When it was injected before the formation of epileptogenic foci the number of convulsions was increased by 30% and the intensity of interictal spikes by 10% (Fig. 1, interval 30-60 min). More marked changes were observed if metamizil was injected after the formation of a focus of epileptogenic activity. Under these conditions convulsions were increased by 40% and spikes by 32% (Fig. 2, interval 90-120 min). Toward the end of the experiment these parameters returned closely to their initial values.

Consequently, eterophen and gangleron possess fairly well-marked anticonvulsant activity and are superior in this respect to phenytoin sodium. The anticonvulsant action of the drugs is exhibited to a greater degree if they are given before the formation of an epileptogenic focus. The results as a whole do not contradict data obtained previously by other workers [7].

The anticonvulsant activity of these drugs is evidently due to their nicotinic cholinolytic properties, for systemic injection of nicotine potentiates the duration of after-discharg-

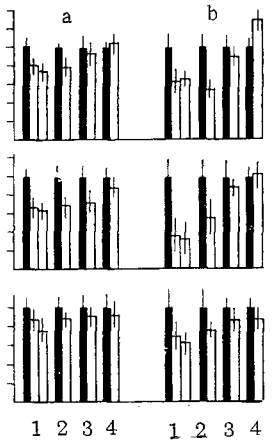

Fig. 1

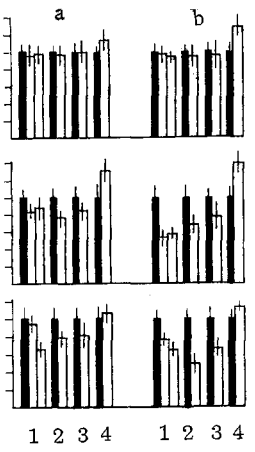

Fig. 2

Fig. 1. Changes in character of epileptogenesis following prophylactic administration of drug (15-20 min before formation of epileptogenic focus in hippocampus). a) Frequency of interictal discharges, b) frequency of convulsions. Abscissa: dark columns — 1) eterophen (5 and 10 mg/kg), 2) gangleron (3 mg/kg), 3) phenytoin sodium (50 mg/kg), 4) metamizil (1 mg/kg); ordinate, intensity of effect (in %). Black columns — control experiments; white columns — effect of drugs.

Fig. 2. Changes in character of epileptogenesis under the influence of drugs administered 30 min after formation of hippocampal epileptogenic focus. Legend as in Fig. 1.

es arising in response to electrical stimulation of the dorsal hippocampus [4] and of convulsions arising after formation of an epileptogenic focus [7]. This hypothesis is supported also by the observations of Gerasimyan [5], who found marked nicotinic cholinolytic properties in more than 20 derivatives of succinimide, including in such well-known antiepileptic agents as zarontin (ethosuximide) and melontin. Phenytoin sodium also has a ganglion-blocking action [9].

Data on the clinical use of gangleron [14] and eterophen [2, 8] in patients with psychomotor epilepsy also confirm the view that compounds with nicotinic cholinolytic properties can be used in the treatment of this disease. However, there are at present very few substances with a "pure" central nicotinic cholinolytic action. Of the known nicotinic cholinolytics, namely gangleron [1], eterophen [12], pediphen (1,1-diphenyl-5-diethylaminopentane) [6], and diphenizide [15], only gangleron is currently available by prescription in the USSR. Eterophen must probably be regarded as an effective anticonvulsant, for it is close to gangleron in efficacy but is less toxic and, unlike gangleron, has no marked ganglion-blocking action.

It can be tentatively suggested that the use of muscarinic cholinolytics as anticonvulsants is not indicated during the initiation of epileptiform activity in structures of the limbic system by whatever method [7, 11] and also in psychomotor epilepsy in man.

Nicotinic and muscarinic cholinergic mechanisms thus play different roles in the formation of epileptiform activity, and the effects of muscarinic and nicotinic cholinolytics differ in direction; this must be taken into account when these drugs are used as anticonvulsants.

LITERATURE CITED

1. N. E. Akopyan, in: Gangleron and Experience of Its Clinical Use [in Russian], Erevan (1959), p. 51.
2. N. N. Anosov, Zh. Nevropatol. Psikhiat., 56, 315 (1956).
3. N. P. Bekhtereva, Neurophysiological Aspects of Human Psychological Activity [in Russian], Leningrad (1974).
4. Yu. S. Borodkin, "Electroencephalographic analysis of the effect of some neurotropic drugs on systems of intracentral regulation and relations between them," Doctoral Dissertation, Leningrad (1967).
5. D. A. Gerasimyan, "The search for new antiepileptic agents among some substituted succinimides," Candidate's Dissertation, Erevan (1971).

6. S. N. Golikov, É. P. Zatsepin, M. A. Levshunova, et al., in: Pharmacology of Central Cholinolytics and Other Neurotropic Agents [in Russian], Leningrad (1969), p. 10.
7. V. A. Gusel', "Experimental study of the efficacy of pharmacological agents which interact with cholinergic systems in psychomotor epilepsy," Doctoral Dissertation, Leningrad (1975).
8. V. A. Gusel' and S. A. Sverdlov, Trudy Leningrad Nauch.-Issled. Psikhonevrol. Inst. im. V. M. Bekhtereva, 68, 45 (1974).
9. I. S. Zavodskaya, in: The Pharmacology of New Therapeutic Agents [in Russian], Leningrad (1953), p. 56.
10. A. N. Zaidel', Elementary Evaluation of Errors of Measurements [in Russian], Leningrad (1968).
11. N. A. Losev, "Pharmacological analysis of α- and β-derivatives of benactyzine and adiphenine," Candidate's Dissertation, Leningrad (1967).
12. N. A. Losev, Farmakol. Toksikol., 35, 544 (1972).
13. N. A. Losev, Fiziol. Zh. SSSR, 44, 1182 (1978).
14. M. Ya. Mikhel'son and Ya. R. Savinskii, Farmakol. Toksikol., 16, 57 (1953).
15. G. F. Rzhevskaya, "Pharmacological properties of phosphorylated acetals, aldehydes, and hydrazides," Doctoral Dissertation, Kazan' (1973).

SEROTONIN TURNOVER IN THYROTOXICOSIS

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An important role in mechanisms of regulation of the function of the endocrine glands, including the thyroid, is played by biogenic amines, among which serotonin is particularly important. Information published on this subject is contradictory: Some data indicate an inhibitory effect of serotonin on thyroid function [1], whereas others support the view that serotonin activates thyroid function and is directly related to the synthesis and secretion of thyroid hormones [2, 3]. Accordingly an unambiguous answer to the question of serotonin turnover in thyrotoxicosis cannot be obtained.

For the above reasons, and also in view of the role of serotonin in the regulation of gastric secretion [4, 5, 8], in the investigation described below the state of the serotonin turnover was studied in experimental thyrotoxicosis.

EXPERIMENTAL METHOD

Mature male Wistar rats weighing 180-200 g were used. Experimental hyperthyroidism was produced by intraperitoneal injection of 2.5 mg/kg of thyroxine daily for 10, 20, or 30 days. Sixteen animals were used in each group. The corresponding volume of physiological saline was injected into control animals, kept under similar conditions. Serotonin-producing (enterochromaffin) cells (EC cells) were identified and their functional activity estimated by the method described previously [6]. EC cells were counted in an area of 1 mm^2 of longitudinal section through the gastric mucosa. The serotonin concentration in the mucosa, in whole blood, and in the gastric juice was determined by the method in [7]. To assess the morphometric and biochemical data, correlation analysis was used. From the total number of correlations, average (coefficient of correlation r = 0.5-0.69), strong (0.70-0.89), and strongest, or functional (0.9-1.0) were selected.

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