LITERATURE CITED

1. L. Kh. Allikmets (L. H. Allikmets), M. Stanley, and S. Gershon, Life Sci., 25, 165 (1979).
2. J. M. Birch, in: Medical Practice, Lancaster (1977), p. 89.
3. C. J. Earley and B. E. Leonard, J. Pharmacol. Methods., 1, 67 (1978).
4. D. W. Gallager, A. Pert, and W. E. Bunney, Nature, 273, 309 (1978).
5. G. Gianutsos and H. Lal, Mod. Probl. Pharmacopsych., 13, 114 (1978).
6. A. Pert, J. E. Rosenblatt, C. Sivit, et al., Science, 201, 171 (1978).
7. S. K. Puri and H. Lal, Psychopharmacologia (Berlin), 32, 113 (1973).
8. S. K. Puri, T. C. Spardling, and C. R. Mantione, Life Sci., 23, 637 (1978).
9. I. S. Sanghvi and S. Gershon, Biochem. Pharmacol., 26, 1183 (1977).

EFFECT OF GABA ISONICOTINOYLAMIDE ON THE CEREBRAL CIRCULATION

R. S. Mirzoyan, T. S. Gan'shina, and L. M. Shmuilovich

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KEY WORDS: GABA isonicotinoylamide; cerebral circulation; nervous regulation of the cerebral circulation.

Gamma-aminobutyric acid (GABA) has a marked effect on the cerebral circulation. It has been found that GABA can increase the blood supply to the brain by lowering the tone of the cerebral vessels [6]. Together with GABA, the walls of the blood vessels have been shown to contain enzymes concerned in its biosynthesis (glutamic acid decarboxylase) and activation (GABA transaminase) [7-9], and receptors sensitive to GABA have been discovered [10-12]. It has also been shown that central GABAergic mechanisms play a role in the regulation of the cerebral circulation [3].

It was accordingly decided to study the cerebrovascular properties of new GABA derivatives. For this purpose, GABA isonicotinoylamide was synthesized [2], and its effect on the cerebral circulation studied.

EXPERIMENTAL METHOD

Experiments were carried out on 27 cats weighing 3-4 kg under general anesthesia (urethane and chloralose), with artificial ventilation of the lungs, and on five waking cats. The cerebral blood flow in the carotid system was determined with the aid of ^{133}Xe on a VAV-100 apparatus and an electromagnetic flowmeter (Nihon Kohden, Japan). The EEG was recorded from the parietal region, the ECG in lead II, and the blood pressure in the femoral artery. Tonic activity and reflex responses in sympathetic nerves of the renal plexus and stellate ganglion were recorded [1]. The vascular component of the action of the compound on the cerebral hemodynamics was differentiated by a technique of separate bilateral perfusion of the carotid and vertebral arteries [4]. The partial pressure of carbon dioxide was determined in samples of arterial blood by the ABC-1 apparatus and it was maintained within the control limits (35-40 mm Hg). The animals were killed with a mixture of urethane and chloralose.

EXPERIMENTAL RESULTS

In the experiments to record the cerebral blood flow by means of an electromagnetic flowmeter and ^{133}Xe it was found that GABA isonicotinoylamide (GABA-INA) in a dose of 10 mg/kg, injected intravenously, increased the cerebral circulation by 34 $\pm$ 4.5%. The effect developed from the first few minutes after injection of the compound and the initial level of the blood flow was restored after 40-60 min. The blood pressure fell by 31 $\pm$ 3.3%.

The study of the effect of GABA-INA (10 mg/kg) on tone of the cerebral vessels by separate bilateral perfusion of the carotid and vertebrobasilar arteries showed that the compound can lower vascular tone equally in the two arterial systems of the brain. In the carotid system the fall in tone amounted to 20 $\pm$ 2.4%, and in the vertebral artery system to 21 $\pm$ 3.5%.

Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.)

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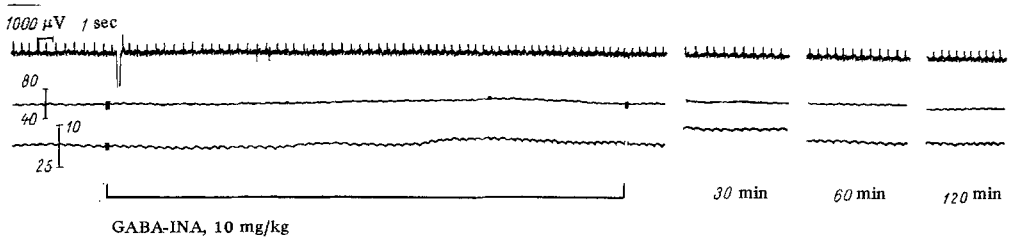

Fig. 1. Effect of GABA-INA (10 mg/kg intravenously) on blood supply to brain in waking cat. From top to bottom: ECG, arterial blood pressure (in mm Hg), blood flow in internal maximally artery (in ml/min), marker injection of compound.

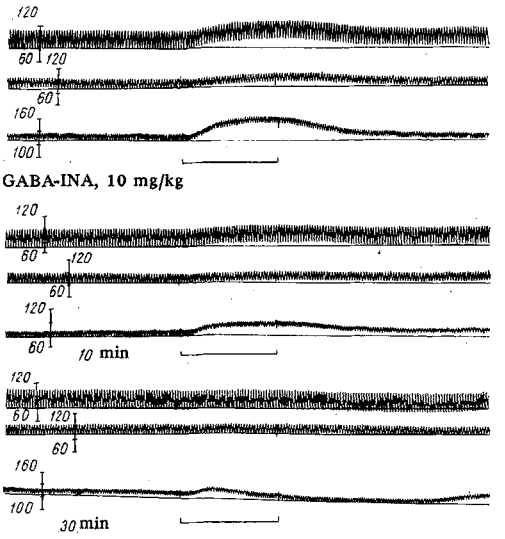

Fig. 2. Effect of GABA-INA (10 mg/kg, intravenously) on constrictor responses of cerebral vessels. Above – control reactions, below – 10-30 min after injection of compound. From top to bottom: perfusion pressure in system of carotid arteries, vertebral arteries, arterial pressure (in mm Hg), marker of stimulation (20 V, 20 stimuli/sec, 1 msec, 15 sec).

In waking animals with a preimplanted transducer of the electromagnetic flow meter, the compound increased the blood supply of the brain by a much greater degree than in cats under general anesthesia, on average by 63 ± 3.1%, and the effect lasted 120-150 min (Fig. 1).

The effect of GABA-INA on nervous regulation of the cerebral circulation also was studied. The compound depressed changes in the cerebral blood flow in the period of formation of the vasomotor reflex by 41 ± 1.2%. Pressor vasomotor reflexes were weakened on average by 30 ± 2.6%.

In a separate series of experiments the effect of GABA-INA on constrictor responses of the cerebral vessels to electrical stimulation of afferent fibers of the tibial nerve was studied. The experiments showed that the compound depresses reflex responses of the vessels equally – of the carotid system by 83 ± 8% and the vertebrobasilar system by 80 ± 9.5% (Fig. 2).

Under the influence of GABA-INA moderate inhibition of tonic activity was observed in the sympathetic nerves of the stellate ganglion and renal plexus, accompanied by a depriming effect on reflex responses in the sympathetic nerves, and potentiation of the inhibitory component of the somatosympathetic responses to high-frequency afferent stimulation. These results point to the ability of GABA-INA to pass through the blood-brain barrier and to act on the central stage of regulation of the cerebral circulation. However, blocking of reflex constrictor responses of the brain vessels may also be due to possible sympatholytic and adrenolytic properties of GABA-INA. To shed light on this problem a separate series of experiments was carried out in which the effect of the compound on the reduction in the cerebral blood flow caused by stimulation of the ipsilateral cervical sympathetic nerve was studied. These experiments showed that GABA-INA did not affect these changes in the cerebral blood flow. Consequently, the compound does not block constrictor responses of brain vessels due to sympathetic nerve stimulation, which indicates that the compound has no central sympatholytic and adrenolytic action.

The investigation thus showed that GABA-INA increases the cerebral circulation and lowers the tone in the two arterial systems of the brain. This effect is more marked in waking cats than in cats under general anesthesia. The compound also lowers the blood pressure. It must also be noted that GABA-INA gives a stronger and more lasting cerebrovascular effect than GABA itself and papaverine [5, 6].

It can be concluded from these results that GABA-INA is a promising drug for clinical use in patients with cerebrovascular disorders.

LITERATURE CITED

1. E. A. Bendikov, L. M. Shmuilovich, and V. M. Kopelevich, Byull. Éksp. Biol. Med., No. 1, 65 (1972).
2. V. V. Zakusov, L. M. Shmuilovich, R. S. Mirzoyan, et al., Author's Certificate No. 789517 (USSR), Otkrytiya, No. 47 (1980).
3. T. S. Gan'shina, Byull. Éksp. Biol. Med., No. 10, 439 (1980).
4. R. S. Mirzoyan, Fiziol. Zh. SSSR, No. 6, 966 (1973).
5. R. S. Mirzoyan and Yu. M. Varentsov, Byull. Éksp. Biol. Med., No. 2, 46 (1973).
6. S. A. Mirzoyan and V. P. Akopyan, in: The Role of Gamma-Aminobutyric Acid in Activity of the Nervous System [in Russian], Leningrad (1964), p. 44.
7. S. A. Mirzoyan, B. A. Kazaryan, and V. P. Akopyan, Dokl. Akad. Nauk SSSR, 186, No. 1, 231 (1969).
8. S. A. Mirzoyan, B. A. Kazaryan, and V. P. Akopyan, Dokl. Akad. Nauk SSSR, 190, No. 5, 1241 (1970).
9. S. A. Mirzoyan, B. A. Kazaryan, and V. P. Akopyan, Dokl. Akad. Nauk SSSR, 214, No. 2, 465 (1974).
10. L. Edvinsson and D. N. Krause, Brain Res., 173, 89 (1979).
11. M. Fijiwara, I. Muramatsu, and S. Shibata, Br. J. Pharmacol., 55, 561 (1975).
12. D. N. Krause, E. Wong, P. Degener, et al., Brain Res., 185, 51 (1980).

EFFECT OF β-ADRENOMIMETICS AND β-ADRENOBLOCKERS ON THE ACTION OF BRADYKININ

G. Ya. Shvarts

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The writer showed previously that the α-adrenoblockers phentolamine and tropaphen reduce the action of bradykinin on extravascular smooth muscles but do not alter the depressor effect of this polypeptide [2]. There is also evidence that the β-adrenoblockers inderal and visken potentiate the depressor effect of bradykinin [1].

The aim of the present investigation was to study the effect of β-adrenomimetics (isoproterenol, orciprenaline, inoline) and also of selective β_1-adrenoblockers (atenolol, practolol) and unselective β_1- and β_2-adrenoblockers (propranolol, pindolol, oxprenolol) on changes in smooth muscle tone, microvascular permeability, and the arterial pressure level caused by bradykinin.

EXPERIMENTAL METHOD

The effect of β-adrenomimetrics (β-AM) and β-adrenoblockers (β-AB) on changes in tone of the extravascular smooth muscle caused by bradykinin was studied on isolated segments of the ileum from guinea pigs weighing 250-350 g. The biphasic response of the intestine to bradykinin (relaxation, giving way to spasm) was recorded under isotonic conditions by means of a balanced pen on the smoked drum of a kymograph.

β-AM and β-AB, dissolved in Krebs' solution, were added in concentrations of between $1 \cdot 10^{-10}$ and $1 \cdot 10^{-5}$ g/ml to the vessel containing the test organ 3 min before bradykinin ($1 \cdot 10^{-8}$ g/ml). The action of each concentration was studied on 5-7 segments of intestine. The experiments results were subjected to statistical analysis.

Laboratory of Pharmacology, S. Ordzhonikidze All-Union Pharmaceutical Chemical Research Institute, Moscow.

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