EFFECT OF GABA-ERGIC AGENTS ON DEVELOPMENT OF NEUROGENIC LESIONS IN THE RAT STOMACH

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An increasingly important role in the development of diseases of the internal organs is being currently ascribed to nervous factors. Research in the Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, has demonstrated the reflex nature and leading role of the sympathetic nervous system in the formation of dystrophic changes in tissues of the stomach, liver, pancreas, and myocardium during exposure to extremal influences [3]. The main stage of the pathogenetic mechanism of development of neurogenic visceral pathology has been shown to be exhaustion of noradrenalin (NA) reserves in the tissues of the internal organs and in the hypothalamic region of the brain [3].

We know that NA is involved in the regulation of energy metabolism, that it significantly affects the course of protein, RNA, and DNA biosynthesis, and that it can behave as a regulator of mitosis [4, 6, 11]. Research in our laboratory has shown that processes of oxidative phosphorylation are uncoupled in the tissue of organs with neurogenic lesions, succinate dehydrogenase and cytochrome oxidase activity is depressed, the concentrations of oxidized forms of nicotinamide nucleotides are reduced, and the mitochondrial membrane potential is depressed [2, 10]. These findings indicate a disturbance of energy formation, which leads to a sharp fall in the creatine phosphate (CP) level and to a smaller fall in the ATP level in the tissues [3]. Slowing of the rate of RNA and DNA synthesis also has been found in tissues of the myocardium and stomach, and also slowing of the incorporation of labeled amino acids into proteins and disturbance of mitotic activity in the gastric mucosa in association with the presence of neurogenic lesions in these organs [3, 8].

The experimental data described below are evidence that exhaustion of tissue NA reserves leads to serious changes in energy and structural metabolism, which themselves leads to considerable disturbances of the functional and structural organization of the organs. Research in our laboratory also has shown that agents capable of restoring activity of the sympathetic nervous system or preventing exhaustion of reserves of its mediator (NA) in the tissues are effective for the pharmacotherapy and prevention of neurogenic lesions of the internal organs [3].

The aim of this investigation was to study the possibility of using the GABA-ergic agents β-phenyl-GABA (fenibut) and piracetam for the pharmacological correction of neurogenic lesions induced in the stomach by exposure to extremal influences. These drugs are known to influence metabolism of biogenic amines, to active bioenergetic processes, and to stimulate protein and nucleic acid synthesis [9, 14].

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 180-200 g, obtained from the "Rappolovo" nursery, Academy of Medical Sciences of the USSR. Neurogenic lesions of the stomach were induced by electrical stimulation of the animals for 3 h through needle electrodes inserted into the forelimb muscles [3]. A current of square pulses, generated by an ÉST-12 electronic stimulator, with output voltage 8 V (to 10 rats), frequency 20 Hz, pulse duration 10 msec, was used for electrical stimulation. Before the experiment all the animals were deprived of food for 2 days. After the end of electrical stimulation concentrations of NA, CP, and malonic dialdehyde (MDA) were determined in the gastric tissues [12, 13, 15].

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TABLE 1. Pharmacologic Correction of Neurogenic Lesions in the Stomach by the Use of Piracetam and β-Phenyl-GABA (M ± m)

Experimental conditions	NA, μg/g	CP, μmoles/g	MDA, μmoles/g	Number of lesions
Control	0,45±0,04 (*n*=8)	1,15±0,08 (*n*=6)	2,72±0,21(*n*=6)	0
Electrical stimulation	0,19±0,03*** (*n*=8)	0,49±0,06*** (*n*=6)	4,79±0,31*** (*n*=6)	5,5±1,1 (*n*=20)
Piracetam + ES	0,40±0,05*** (*n*=8)	1,05±0,06*** (*n*=6)	2,74±0,30*** (*n*=6)	1,1±0,37** (*n*=20)
Piracetam	0,43±0,03 (*n*=8)	1,01±0,08 (*n*=6)	3,12±0,12 (*n*=6)	0 (*n*=20)
β-Phenyl-GABA + ES	0,42±0,04*** (*n*=8)	1,14±0,14*** (*n*=6)	2,72±0,21*** (*n*=6)	2,6±0,82* (*n*=19)
β-Phenyl-GABA	0,38±0,05 (*n*=8)	1,18±0,11 (*n*=6)	2,80±0,19 (*n*=6)	0 (*n*=20)

Note. n) Number of experiments; *p < 0.05, **p < 0.002, ***p < 0.001. Results following administration of drug + electrical stimulation compared with results of electrical stimulation alone; remaining results compared with control.

The severity of the lesions in the gastric mucosa was assessed by the number of destructive lesions per animal on average in each group. Pharmacological correction was carried out with the cyclic GABA analog piracetam and the phenyl GABA analog fenibut in doses of 50 mg/kg. The compounds were injected intraperitoneally 30 min before the beginning of electrical stimulation. Intact animals served as the control.

EXPERIMENTAL RESULTS

The experimental results (Table 1) showed that electrical stimulation caused the formation of hemorrhagic erosions in the gastric mucosa, numbering on average 5.5 ± 1.1 per animal. Meanwhile the NA level in the gastric wall showed a decrease from 0.45 ± 0.04 to 0.19 ± 0.03 μg/g. Together with lowering of the NA level, exposure to electrical stimulation led to a decrease in the concentration of the high-energy compound CP by 57% compared with the control.

Many investigators currently ascribe the key role in the realization of stress to lipid peroxidation (+PO). It has been shown, for instance, that as a result of acute and chronic emotional-painful stress, primary and secondary LPO products accumulate in the cells, leading to damage to membrane structures [7]. It must be recalled, however, that activation of LPO under pathological conditions may be secondary and due to disturbances of function of the sympathicoadrenal system and of energy-forming processes [5].

Our experiments demonstrated that electrical stimulation for 3 h, causing disturbance of integrity of the gastric mucosa, increased the MDA concentration by 76% compared with the control, evidence of activation of LPO in the stomach tissues.

Piracetam, injected before the beginning of electrical stimulation, appreciably protected the gastric muscosa and reduced the formation of hemorrhagic erosions from 5.5 ± 1.1 to 1.1 ± 0.37 per animal. This compound considerably prevented exhaustion of the NA reserves in the stomach wall, so that they were close to the control level. Piracetam prevented the fall in the CP concentration and increased the MDA concentration also.

Fenibut had a rather weaker protective action on the gastric mucosa than piracetam. The number of destructive lesions in the mucosa of the experimental animals with β-phenyl-GABA was 2.6 ± 0.82 on average per animal. β-Phenyl-GABA, like piracetam, prevented exhaustion of the NA reserves, the decrease in the CP concentration, and activation of LPO in the stomach wall of rats exposed to electrical stimulation.

Previous investigations showed that electrical stimulation of rats for 3 h leads to a fall of the GABA concentration in the hypothalamic region [3]. An essential role in activation of the natural mechanisms of adaptive, protective character is nowadays ascribed to the GABA-ergic system [1]. This is on account of the fact that GABA is involved in the regulation of neuronal activity and the modulation of endocrine shifts, and it is functionally linked with other neurotransmitter systems. The GABA insufficiency which we observed in the hypothalamic region of the brain, together with exhaustion of NA reserves, under extremal conditions may led to disturbance of the mechanisms of adaptation and to the development of dystrophic lesions in the gastric mucosa. Piracetam and β-phenyl-GABA, whose effects are linked with activation of the GABA-ergic system, improving the course of neurotransmitter processes and of energy and structural metabolism, increased the resistance of the body to extremal influences. This range of properties of piracetam and β-phenyl-GABA means that these compounds may be used not only to prevent, but also to treat diseases in whose development the nervous factor plays the leading role.

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SELECTIVE EFFECT OF NEUROLEPTICS ON DOPAMINE-DEPENDENT BEHAVIORAL DISTURBANCES IN RATS IN THE EXTRAPOLATION ESCAPE TEST

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The detection of antidopaminergic activity is a basic trend in neuroleptic screening. For this purpose the ability of substances to affect stereotyped behavior of rodents, induced by dopamine (DA) receptor agonists apomorphine, amphetamine, and L-dopa, has been studied [15]. Many known neuroleptics with phenothiazine and butyrophenone structure reduce, whereas classical antidepressants increase the intensity and duration of stereotyped reactions [9]. However, an atypical character of action of neuroleptics and antidepressants has been found in a series of benzamide derivatives. For instance, different doses of sulpiride and tiapride exhibit (according to clinical data) neuroleptic and antidepressive activity [7, 10]. However, the dose range within which they weaken stereotyped climbing on a net and strengthen stereotypy induced by amphetamine is identical [9, 15]. The antiemetic metoclopramide and the sedative sultopride have virtually no antipsychotic action [11, 15], but nevertheless they inhibit all forms of apomorphine and amphetamine stereotypy much more effectively than sulpiride [9, 15].

In view of these facts it is essential to discover more selective screening methods for neuroleptics and to make a more penetrating study of the mechanism of their antipsychotic effect. One approach to the solution of this problem is to study the effect of neuroleptics on memory processes, on the mechanisms of positive and negative reinforcement, and also on other complex psychological phenomena [13].

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