TREATMENT OF EXPERIMENTAL DESTRUCTIVE LESIONS OF THE DUODENUM BY NOOTROPICS

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Recognition of a separate group of drugs with nootropic type of action as compounds improving integrative activity of the brain and increasing its resistance to harmful external environmental influences [11] has stimulated the study of various aspects of the action of nootropics on the body. The effect of nootropics on the CNS has received the most study [12]. The mechanism of action of nootropics is through improvement of energy-related processes in the tissues, stimulation of RNA and protein synthesis, acceleration of turnover of mediators and of the most important amino acids, and improvement of the microcirculation [8]. This means that nootropics exhibit effects that are related equally to nerve tissue and to the internal organs. It must be emphasized that clinicians have achieved more definite success than experimental workers with the use of nootropic drugs for the treatment of many diseases of the internal organs, including peptic ulcer [2, 3]. The group of nootropics combines a fairly considerable number of drugs (pyracetam and its analogs, GABA derivatives, preparations of ergot, etc.), although it is pyracetam which has been used and studied most widely at the present time.

The aim of this investigation was to study the therapeutic efficacy of the nootropic drugs pyracetam and ethimizole and to compare it with that of cholinolytics (oxyphenonium), tissue repair promoters (solkoseryl) and histamine H_2-receptor antagonists (cimetidine) in experimental destructive lesions of the duodenal mucosa, and also their effect on parameters of energy metabolism (creatine phosphate concentration) in this form of pathology.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male rats weighing 180-200 g. Destruction of the duodenal mucosa was stimulated by application of two Pean's forceps to the pyloric part of the stomach and to the jejunum (at a distance of 9-10 cm from the pylorus) for 15 min by a modified method in [9]. The animals were killed 3-4 h and 1, 2, 3, 4, 5, 6, and 7 days after injury by the forceps. Under a binocular loupe the number of destructive lesions (erosions and ulcers) were counted on the surface of the duodenal mucosa (a segment 8-9 cm long was taken from the pylorus), and their area was determined separately in three regions: proximal, middle, and distal, each 2.5-3 cm long. The first destructive lesions were formed 3-4 h after trauma (Fig. 1). The maximal degree of injury to the mucosa was recorded after 24 h; later the number of destructive lesions decreased and none were observed on the 5th-6th day after the operation. Histological investigation of the duodenal tissue 48 h after trauma revealed destructive lesions in it. At sites of destruction the mucosa was denuded of epithelium, dense infiltration of the submucosa by lymphocytes and leukocytes were observed, and its veins were congested with blood. Treatment of the experimental lesions began two days after trauma. The course of treatment consisted of six injections of the test preparations with intervals of 8-10 h between injections. All injections were given subcutaneously in a volume of not more than 0.5 ml. The treated animals were killed 56-60 h after trauma. In a parallel series of experiments the creatine phosphate concentration was determined in the duodenal tissue [10]. The drugs used for pharmacological analysis were pyracetam (Nootropil, from "Polfa," Poland; 200 mg/kg), ethimizole (3 mg/kg) and solkoseryl ("Alkaloid-Skopje," Yugoslavia; 0.5 ml/kg), oxyphenonium bromide (5 mg/kg), and cimetidine (Tagamet, Smith, Kline, and French, USA;

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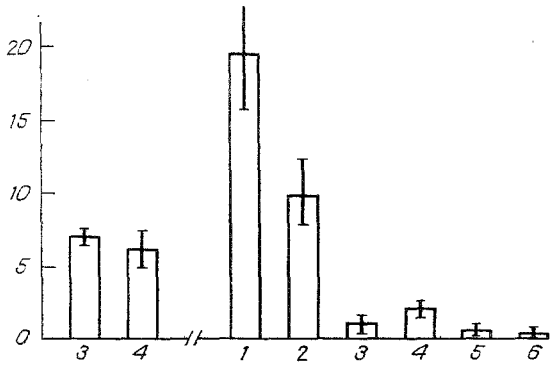

Fig. 1

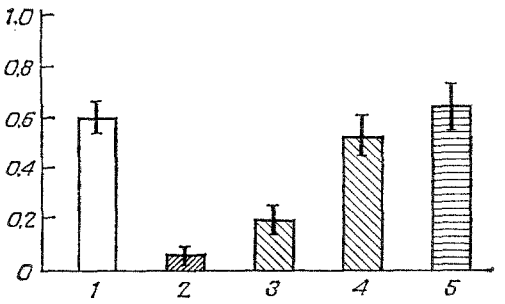

Fig. 2

Fig. 1. Time course of development of destructive lesions of the duodenum. Ordinate, area of destructive lesions of mucosa (in mm^2/cm^2); abscissa, time (in h on left, in days on right).

Fig. 2. Creatine phosphate concentration in duodenal tissue after trauma and pharmacotherapy. Ordinate, creatine phosphate concentration (in μmoles/g tissue); abscissa, groups of rats: 1) control, 2) trauma, 3) trauma + solkoseryl 4) trauma + pyracetam, 5) trauma + ethimizole.

25 mg/kg). Control animals received 0.9% sodium chloride solution. The number of animals in each series of experiments was 8-12. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

In the control rats subjected to duodenal trauma, on average 5.3 ± 0.7 destructive lesions were recorded after 48 h, mainly in the proximal part of the duodenum (Table 1). The total area involved was 7.1 ± 1.1 mm^2, of which 5.8 ± 0.7 mm^2, i.e., 78% of the total area, was accounted for by destruction of the proximal portion. The most therapeutically effective of the nootropics were pyracetam (200 mg/kg) and ethimizole (3 mg/kg): after a course of treatment no experimental destructive lesions were observed in any of the animals. Solkoseryl (0.5 ml/kg) and, to a lesser degree, cimetidine (25 mg/kg) and oxyphenonium bromide (5 mg/kg) also had therapeutic activity, although it was much weaker than that of pyracetam and ethimizole ($p = 0.05-0.01$).

The results were correlated with investigations of the creatine phosphate concentration in the duodenal tissue. The creatine phosphate concentration was reduced ninefold 48 h after trauma (Fig. 2). A course of treatment with pyracetam and ethimizole restored the initial creatine phosphate level, whereas administration of solkoseryl increased it threefold, but the level in the control (intact) animals was not reached.

Treatment of experimental destructive lesions of the duodenum in rats thus showed the nootropics pyracetam and ethimizole to be therapeutically highly effective, and this correlates strongly with their ability to restore the creatine phosphate level in the tissues of the affected duodenum.

Many experimental models of peptic ulcer exist [6]. For the duodenum we chose and adapted a model in whose pathogenesis several stages can be distinguished. First, there is an excessive flow of nervous impulses, inducing intensive release, followed by exhaustion of catecholamines in sympathetic nerve endings [7]; second, a marked disturbance of the microcirculation due to mechanical compression of two areas of the gastrointestinal tract (by application of Pean's forceps) and subsequent edema of the mucosa and submucosa; finally, increased production of biologically active substances (histamine, kinins, vasointestinal peptide, etc.) and their local damaging action on the intestinal mucosa [6]. With this multistaged genesis of development of destructive lesions of the duodenum, the therapeutic action of drugs of several different classes (cholinolytics, histamine H_2-receptor antagonists, tissue repair promoters, energizers, and so on) may perhaps be effective. In fact, in the present experiments the different drugs gave a healing effect through their action on different stages of pathogenesis of experimental ulcers. For instance, the muscarinic cholinolytic oxyphenonium reduce

TABLE 1. Therapeutic Efficacy of Drugs in Experimental Destructive Lesions of the Rat Duodenum

Preparation, dose	Number of destructive lesions				Area of lesion, mm^2			
	total	proximal portion	middle portion	distal portion	total	proximal portion	middle portion	distal portion
Control (physiological saline)	5,3±0,7	2,2±0,6	1,3±0,5	1,8±0,6	7,1±1,1	5,8±0,7	0,5±0,3	0,8±0,2
Oxyphenonium bromide, 5 mg/kg	1,0±0,2*	0,7±0,2*	0,1±0,1*	0,2±0.1**	1,6±0,4*	0,9±0,7*	0,3±0,2	0,4±0,1
Solkoseryl, 0.5 ml/kg	0,1±0,1**	0,1±0,1**	0**	0**	0,3±0,3**	0,3±0,3**	0*	0*
Cimetidine, 25 mg/kg	0,5±0,1*	0,1±0,1**	0,1±0,1**	0**	1,4±0,3*	1,0±0,6*	0,4±0,2	0*
Pyracetam, 200 mg/kg	0***	0**	0**	0**	0**	0**	0*	0*
Ethimizole, 3 mg/kg	0***	0**	0**	0**	0**	0**	0*	0*

Legend. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

the enhanced nervous impulsation in cholinergic neurons (mainly in the system of the vagus nerve), the histamine H_2-receptor antagonists cimetidine protected the mucosa against the aggressive action of histamine, and the tissue repair promoter solkoseryl restored normal metabolism in the intestinal wall. It must be emphasized that all three drugs had basically a local action, whereas the nootropic compound pyracetam and ethimizole had both local and a central action.

It follows from the literature devoted to analysis of the mechanisms of action of nootropics on the principal systems and functions of the body that the effects of these compounds are linked primarily with activation of energy metabolism, stimulation of macromolecular synthesis, a normalizing influence on mediator protein, and lipid metabolism, and their antianoxic action [8]. Thus pyracetam and ethimizole raise the creatine phosphate level in brain, heart, liver, and stomach tissues [7, 11], stimulate uptake of local precursors of RNA and protein synthesis into nuclear RNA and total protein of the brain and stomach [5, 14], inhibit phosphodiesterase [7, 13], and raise the cyclic AMP level in the tissues [5, 6, 15], improve synaptic transmission in neurons [4, 8], and have an antianoxic action on models of anoxic and circulatory anoxia [1, 8]. Such a wide spectrum of properties of the nootropics makes them preparations of choice for the treatment of exacerbations of peptic ulcer also. As the present investigation shows, pyracetam and ethimizole exhibit greater therapeutic activity than the other drugs tested in the treatment of experimental destructive lesions of the duodenum, and this fact correlates with their ability to restore the lowered creatine phosphate level in its tissue. These data are confirmed by clinical observations [2, 3] which show that pyracetam and ethimizole have good therapeutic properties in the treatment of patients with exacerbation of duodenal ulcer. Hence it can be concluded that nootropics should be added to the list of therapeutic preparations used in the treatment of exacerbations of duodenal ulcer.

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