COMPARATIVE INHIBITORY ACTION OF A PSYCHOSTIMULANT OF THE SYDNONEIMINE SERIES OF DEVELOPMENT OF STRESS- AND ETHANOL-INDUCED DAMAGE TO THE GASTRIC MUCOSA IN RATS

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It has recently been shown that sydnophen, a Soviet preparation of the phenylalkylsydnoneimine series, which has been used for a long time in medical practice as a psychostimulant, with simultaneous antidepressive activity [1, 2], has a marked peripheral vagolytic action [6-8]. Since it inhibits parasympathetic chronotropic responses of the heart in different classes of vertebrates [6, 8] it can be regarded as a drug capable of modulating parasympathetic regulation of the cardiac rhythm [6].

It is logical to suggest that some modulators of the cardiovascular system will transform the function of other systems of the body also, including in certain pathological states. The possibility cannot be ruled out that preparations of the group mentioned above, which have a combined action both on central structures and on peripheral parasympathetic mechanisms, can be used to prevent and treat various diseases whose mechanism of origin is linked to some degree or other with central subcortical influences, realized through the autonomic nervous system and also with purely peripheral mechanisms. One such pathological state is gastric ulcer.

In this investigation we studied the effect of OF743, a psychostimulant of the sydnoneimine series, and which, like sydnophen blocks parasympathetic chronotropic effects on the heart, on experimentally induced lesions of the gastric mucosa in rats. In its structure OF743 contains components similar to catecholamines.

EXPERIMENTAL METHOD

Injuries to the gastric mucosa were produced in male rats weighing 200-220 g by combined immobilization and cold stress [9] or by injection of absolute ethanol into the stomach in a dose of 1 ml/100 g body weight [10]. The animals were deprived of food for 24 h before immobilization or injection of ethanol, but access to water was unrestricted when the damage was caused by the first method, and rats on which the second method was used were deprived of water for 18 h before injection of ethanol The investigations were conducted simultaneously on two groups of animals: control and experimental (five rats in each group). Rats of the control group were given an intramuscular injection of 0.2 ml of physiological saline and the experimental animals received the preparation OF743 in a volume of 0.2 ml and in doses of 0.001-25 mg/kg body weight 24 and 1 h before immobilization or injection of ethanol. Damage to the mucosa was calculated in millimeters under a binocular loupe and was estimated in accordance with a modified 3-point system. Three parameters were used for the size of the lesion: the severity of the damage (SD) (the size of the lesion was estimated in points), the frequency of the lesion – FL (the ratio of the number of rats with damage to the number of animals in the given group, and the ulcer index – UI (UI = SD + 2FL). The results were analyzed by nonparametric statistical tests. Regression of the lesions was calculated relative to the degree of damage in the control, taken as 100%.

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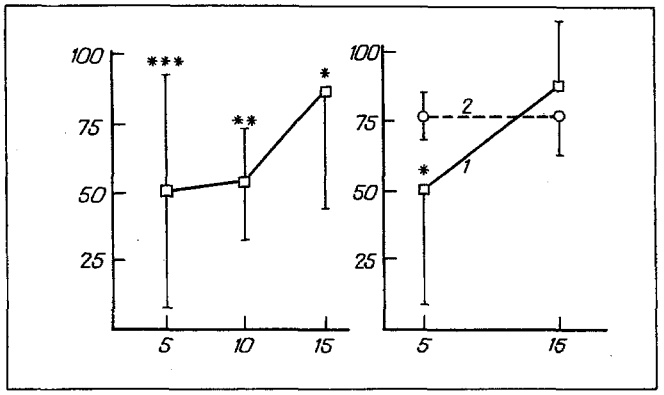

Fig. 3 Fig. 4

Fig. 1. Dose-dependence of reduction in severity of damage to gastric mucosa induced by immobilization and cold stress following injection of the psychostimulant OF743. Here and in Figs. 2 and 3: abscissa: dose of OF743 given by intramuscular injection (in mg/kg); ordinate, decrease in severity of damage. *$p < 0.05$, **$p < 0.005$, ***$p < 0.001$.

Fig. 2. Comparison of decrease in severity of damage to gastric mucosa induced by combined immobilization and cold stress and by intragastric injection of ethanol in animals treated with OF743. 1) Stress, 2) ethanol. *$p < 0.05$.

EXPERIMENTAL RESULTS

In 55 of 56 rats of the control group, after combined immobilization and cold stress lesions were observed in the gastric mucosa, in the form of hemorrhages and erosions, varying in length from 1-2 to 4 mm or more. If the rats were given 15 mg/kg of OF743 before exposure to immobilization and cold stress, there were no lesions visible in seven of the 19 rats, and in the rest they were much less severe. The inhibitory action of OF747 on stress-induced damage to the mucosa was dose-dependent (Fig. 1).

Thus OF743 inhibits damage induced by combined immobilization and cold stress, in the initiation of which an important role is played by central mechanisms It can be tentatively suggested that the inhibitory action of OF743 is realized at the cortical and subcortical levels, where the psychostimulant effect of the drug is realized, and also at the periphery.

In the next series of experiments the possible inhibitory action of OF743 was studied on lesions caused by absolute ethanol (intragastric injection). We postulated that, unlike lesions induced by stress, the basic mechanisms responsible for ethanol-induced lesions of the gastric mucosa are peripheral mechanisms.

Lesions arising in the gastric mucosa following injection of ethanol were quite different in character: they were elongated, quite narrow hemorrhages and erosions. In our experiments, lesions were detected in all control rats. Injection of ethanol against the background of OF743 in a dose of 15 mg/kg in 14 of the 30 rats was not accompanied by any damage to the mucosa, but in the remaining rats, the lesions were much more severe. The inhibitory action of OF743 in relation to ethanol-induced damage was dose-dependent. The lowest dose giving rise to a significant reduction of 30% in SD, was 0.01 mg/kg.

Comparison of the dose-dependence curves showing the decrease in severity of damage to the gastric mucosa caused by combined immobilization and cold stress and by ethanol showed that if the dose was relatively high (15 mg/kg) there was a tendency toward a rather greater decrease in the severity of the stress-induced damage. According to data in the literature, this dose not only blocks parasympathetic pathways, but also gives a psychostimulant effect [6]. With a dose of 5 mg/kg, which on intramuscular injection does not give rise to a central effect, a much greater decrease in the severity of the lesions was observed in the case of ethanol injections: initially the decrease was about 80%, whereas lesions induced by

stress were reduced only by 50% (Fig. 2). The reason probably is that activation of subcortical mechanisms is almost of no significance in ethanol-induced damage compared with stress-induced lesions.

In the next stage of the investigation we compared the action of OF743 with the antiulcerogenic effects of preparations familiar and used for a long time in the treatment of patients with ulcers, namely atropine sulfate and pirenzepine (Gastrozepin). We compared the effects of atropine, pirenzepine, and OF743 on prevention of the development of ethanol-induced damage to the gastric mucosa in rats Atropine and pirenzepine, like OF743, were injected 24 and 1 h before injection of ethanol. The results showed that pirenzepine in doses of 5-15 mg/kg had a weaker inhibitory action on mucosal damage than atropine and OF743. Differences between effects of atropine and OF743 were not significant: in small doses (up to 1 mg/kg) atropine had a tendency to prevent the development of lesions which was stronger than that of OF743, whereas in large doses, OF743 had a tendency to exert a stronger protective function. Incidentally, the weakness of the antiulcerogenic effect of the M1 anticholinesterase drug pirenzepine can be attributed to the fact that mainly M2 anticholinesterase drugs are involved in the formation of ethanol-induced gastric ulcers This is in agreement with data in the literature showing that M2 acetylcholine receptors of glandular type are located principally in the stomach, and M1 acetylcholine receptors are present there only in small numbers [4, 5].

OF743, inhibiting ethanol-induced damage to the same degree as atropine, probably does not possess selectivity toward M1 acetylcholine receptors, but binds also (or solely) with M2 acetylcholine receptors. It has been suggested that OF743, like sydnophen, binds selectively with one subpopulation of M2 acetylcholine receptors [6], i.e., that compared with atropine, it exhibits rather greater selectivity toward M2 acetylcholine receptors, as is shown, for example, by the lesser degree of dilatation of the pupils in response to its injection. It can accordingly be postulated that OF743, which possesses equal antiulcerogenic activity, may give rise to fewer side effects than atropine.

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