Gastroprotective Effect of Zinc Sulfate in Ethanol-Induced Ulcerogenesis in Rats

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In a rat model of ethanol-induced peptic ulcer it is demonstrated that pretreatment with zinc sulfate (intragastral administration) lowers the ethanol-induced damage to the gastral mucosa in a dose-dependent manner. Subcutaneous injection of indomethacin has no appreciable effect on the gastroprotective effect of zinc. It is assumed that the gastroprotective effect of zinc sulfate is not mediated by the release of endogenous prostaglandins.

Key Words: *gastroprotective activity; zinc sulfate; ethanol-induced ulcerogenesis; prostaglandins*

Recently, the antiulcer activity of zinc-containing compounds has attracted considerable interest. Some of them (zinc acexamate, a chelating complex of zinc and L-carnosine, and zinc monoglycerolate) have been recommended for clinical application as drugs with antiulcer or specific gastroprotective activity [5,6,8]. Although the nature of the antiulcer activity of zinc-containing compounds has been extensively studied, the mechanisms of this activity are still obscure.

Noticeable alterations in inc homeostasis - a considerable increase in zinc concentration in the gastral mucosa (GM), a decrease in the plasma Zn content during disease exacerbation, and normalization of these parameters during remission - have been noted in patients with peptic ulcer [1,2]. The diverse changes in Zn content in the GM and plasma during the active stage of ulcerogenesis may result from a redistribution of the metal in the organism caused by the increased demands for healing of the ulcer.

We examined the effect of zinc sulfate on (ZS) on ethanol-induced ulcerogenesis in rats and the possible involvement of endogenous prostaglandins in ZS protection of the GM.

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MATERIALS AND METHODS

Experiments were performed on outbred male albino rats weighing 135-160 g maintained in cages with a bottom area of 2145 cm^2 (10 rats in each cage) at 21-22°C under the standard 12-h lighting regime and with free access to food and water. The animals were fasted for 24 h before the experiment in individual cages with wire bottoms (for the prevention of coprophagy) with free access to water. One hour before induction of peptic ulcer they were injected with distilled water (control group) or aqueous ZS solution ($ZnSO_4 \times 7H_2O$, 5 ml/kg). Ulceration of the GM was induced by intragastral administration of 96% ethanol (1 ml) [11]. In a separate experimental series, the synthesis of endogenous prostaglandins was inhibited with indomethacin injected in a dose of 5 mg/kg subcutaneously, 30 min prior to administration of distilled water or ZS.

The rats were euthanized by ether overdosage 1 h later. The esophagus and pylorus were ligated, and the stomach was incised, filled with formaldehyde (8 ml of 2% solution) using a syringe and

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TABLE 1. Antiulcerogenic Effect of ZS in Modeled Ethanol–Induced Peptic Ulcer in Rats

Group	Number of animals	Dose, mg/kg	Total length of GM damage, mm	Inhibition, %
Control	10	–	53.2±8.9	–
ZS	10	12.5	36.2±4.5	32.0
	10	25	26.2±2.8*	50.8
	10	50	7.7±1.1**	85.5
Pretreatment with indomethacin				
Control	10	–	61.4±9.5	–
ZS	10	50	24.0±5.7*	60.9

Note. One asterisk indicates $p<0.01$, two asterisks $p<0.001$ compared with the control.

placed for 10 min in 2% formaldehyde for fixation of the gastric wall. The stomachs were opened along the greater curvature. The total length of ulcer damage to the GM was measured under an MBS-9 microscope at an 8-fold magnification.

Statistical analysis was performed with the use of Student's *t* test.

RESULTS

The data on the effect of ZS on ethanol-induced ulcerogenesis in rats are summarized in Table 1.

Intragastral administration of ZS reduced in a dose-dependent manner (doses 12.5-50 mg/kg) the severity of ethanol-induced damage to the GM (ID_{50} was about 25 mg/kg). Subcutaneous injection of indomethacin in a dose of 5 mg/kg induced no significant changes in the ulcer index in the control group, which is consistent with the observations of others [3,7].

Compounds producing a slight irritating effect on the GM (for example, dilute ethanol or hydrochloric acid solutions) exhibit gastroprotective activity in the presence of potent necrotizing agents (the phenomenon of adaptational cytoprotection). The protective activity of weak irritants is believed to be associated with the stimulation of the synthesis of endogenous prostaglandins, since it is completely abolished by indomethacin [4,9]. In this study, indomethacin injected in the dose that, according to the literature, provides complete inhibition of prostaglandin biosynthesis in rat GM [10] by inhibiting cyclooxygenase activity [4] did not eliminate the antiulcerogenic effect of ZS, indicating that the antiulcer activity of ZS in experimental ethanol-induced peptic ulcer does not result from the release of endogenous prostaglandins caused by irritation of the GM.

Thus, we found ZS to have a dose-dependent gastroprotective effect in ethanol-induced ulcerogenesis in rats. This effect is not mediated by prostaglandins.

REFERENCES

1. K. L. Erzinkyan, M. V. Lukasheva, S. D. Gobedzhashvili, *et al., Ros. Med. Zh.*, № 5-12, 14-15 (1992).
2. M. V. Lukasheva, K. L. Erzinkyan, S. D. Gobedzhashvili, *et al.*, in: *Evaluation of the Pharmacological Activity of Chemicals: Principles and Approaches* [in Russian], Part 2, Moscow (1989), p. 192.
3. P. Bhandre, R. Diniz-D'Souza, A. Mainker, and V. Dhume, *Europ. J. Pharmacol.*, **191**, 167-172 (1990).
4. T. K. Chaudhury and A. Robert, *Dig. Dis. Sci.*, **25**, 830-836 (1980).
5. G. Escolar and O. Bulbena, *Drugs Exp. Clin. Res.*, **15**, 83-89 (1989).
6. M. Ito, T. Tanaka, and Y. Suzuzki, *Jap. J. Pharmacol.*, **52**, 513-521 (1990).
7. Y. Kurebayashi, Y. Tubuchi, and M. Akasaki, *Arzneimittelforschung*, **39**, 250-253 (1989).
8. K. D. Rainsford and M. W. Whitehouse, *J. Pharm. Pharmacol.*, **44**, 476-482 (1992).
9. A. Robert, J. E. Nezamis, C. Lancaster, *et al., Amer. J. Physiol.*, **245**, G113-G118 (1983).
10. J. L. Wallace, D. R. McCready, B. C. Chin, *et al., Clin. Biochem.*, **17**, 179-184 (1984).
11. G. Zuccari, G. Clavenna, A. Sala, *et al., Europ. J. Pharmacol.*, **187**, 19-25 (1990).