PHYSIOLOGY

Antiulcer Activity of OF-900, OF-743, and Their Combination in Different Rat Models of Peptic Ulcer

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The sydnonimine compounds OF-743, OF-900, and their combination were analyzed for antiulcer activity in three rat models of peptic ulcer induced by ethanol, indomethacin, or stress. The combination, but not individual preparations, strongly inhibited ulcer formation in all models regardless of the season when the study was carried out.

Key Words: *sydnonimines; ulcer formation*

The phenylalkylsydnonimine preparations OF-900 and OF-743 have been used in medical practice: OF-900 as a peripheral vasodilator [8] and OF-743 as an antidepressant and psychostimulant [1]. Our experiments showed that these drugs also produce antiulcer effects [3,5]. In the present study we compared the effects of OF-900 and OF-743 in three rat models of peptic ulcer and estimated antiulcer activity of their combination.

MATERIALS AND METHODS

Experiments were performed on random-bred male albino rats (body weight 170-200 g) in which peptic ulcer was induced by ethanol [9], indomethacin [7], or forced swimming stress [4]. The animals were deprived of food and water for 24 h before administration of ulcerogenic agent. Ethanol (1 ml 96°/200 g body weight) and indomethacin dissolved in physiological saline (60 mg/kg, 1 ml per rat) were administered intragastrally. The rats were euthanized 1 h after ethanol and 6 h after indomethacin. Stress was produced by 1-h swimming in warm water (21-23°C).

Both preparations were dissolved in normal saline and administered intragastrally in a dose of 0.02-20 mg/kg and a volume of 1 ml per rat 24 h and 1 h before administration of ulcerogenic agent. Control rats were given 1 ml normal saline.

Each experimental series (ethanol, indomethacin, and stress) included 5-12 tests and several groups of 5-10 rats.

The severity of damage (SD) to gastric mucosa was estimated by calculating the total length (in mm) of all mucosal lesions, and the antiulcer activity was expressed as the difference (%) in SD between experimental and control rats. The significance of differences was evaluated by nonparametric Wilcoxon—Mann—Whitney *U* test [2].

RESULTS

This study confirmed antiulcer activity of OF-900 and OF-743 [3,5]: both preparations were effective against ulcer formation in all models after intragastral administration (Figs. 1-3).

In indomethacin-treated and stressed rats, much higher doses of OF-900 and OF-743 were necessary to achieve significant inhibition of ulcer formation than in ethanol-treated rats. In the ethanol model, antiulcer effects were observed after the lowest doses: 0.02 mg/kg OF-900 decreased SD by 31% and OF-743 by 11% (Fig. 1). For example, at 10 mg/kg OF-900 decreased SD only by 23% in the indomethacin model during the fall-winter period.

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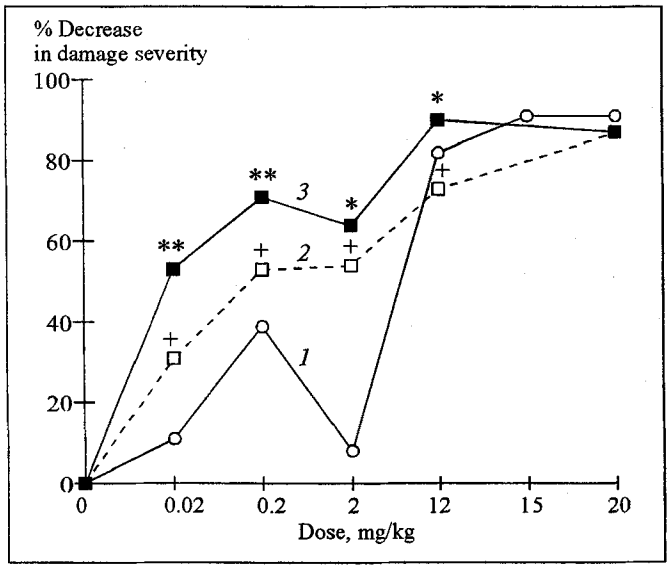

Fig. 1. Effects of OF-743 (*1*), OF-900 (2), and their combination (3) on ethanol-induced peptic ulcer. *$p<0.05$, **$p<0.01$ compared with OF-900; +$p<0.05$ compared with OF-743.

Moreover, antiulcer activity of OF-900 and OF-743 in the indomethacin and stress models strongly depended on the season: in a dose of 20 mg/kg they decreased SD by 44% and 55%, respectively, in September-February, while in March-May they exacerbated the damage to gastric mucosa (Fig. 2).

Bearing in mind the weak antiulcer effects of OF-900 and OF-743, the necessity of administering them in high doses (20 mg/kg) to indomethacin-treated and stressed rats, and the differences between their mechanisms of action (OF-900 acts as a vasodilator [8] and OF-743 acts as a central antidepressant and peripheral cholinolytic [1,6], we decided to examine the effect of OF-900—OF-743 combination. It was found that this combination is much more potent than each preparation. Synergism was particularly strong in the ethanol model, where OF-743 and OF-900 were used in a dose range of 0.02-2 mg/kg. The lowest dose decreased SD by 50%, i.e., had an antiulcer effect achieved upon individual administration of the drugs in doses 10- to 100-fold higher (0.2-2 mg/kg, Fig. 1).

The combination was much more effective in indomethacin and stress models during spring, decreasing SD by 60% (Figs. 2 and 3).

When administered together, OF-900 and OF-743 acted as synergists and markedly inhibited ulcer formation in three rat models regardless of the season. Thus, the OF-900—OF-743 combination is much more effective than individual drugs.

Combined administration of OF-900 and OF-743 makes it possible to reduce their doses, thereby preventing adverse reactions. Since OF-900 and OF-743 have received permission for clinical application, the additional trials necessary for clinical application of these drugs in combination can be carried out using a simplified protocol.

This study was performed in the framework of New Drugs program.

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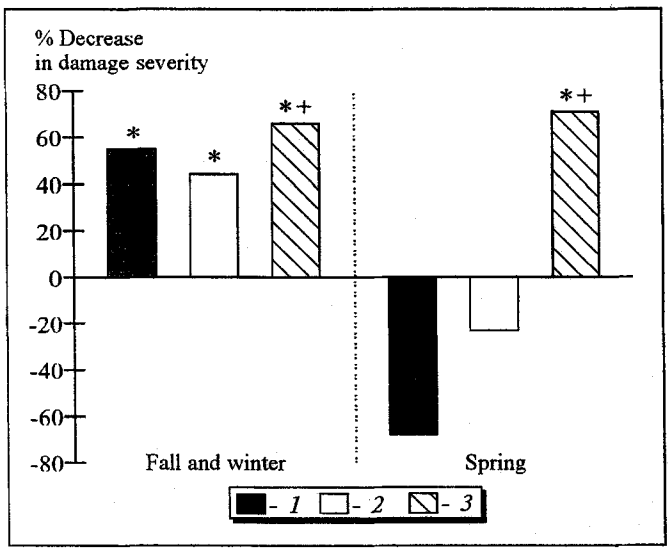

Fig. 2. Effects of OF-743 (20 mg/kg, *1*), OF-900 (20 mg/kg, 2), and their combination (3) of on indomethacin-induced peptic ulcer. $p<0.05$: *compared with the control; +compared with OF-900. Negative values indicate increased severity of damage in comparison with the control.

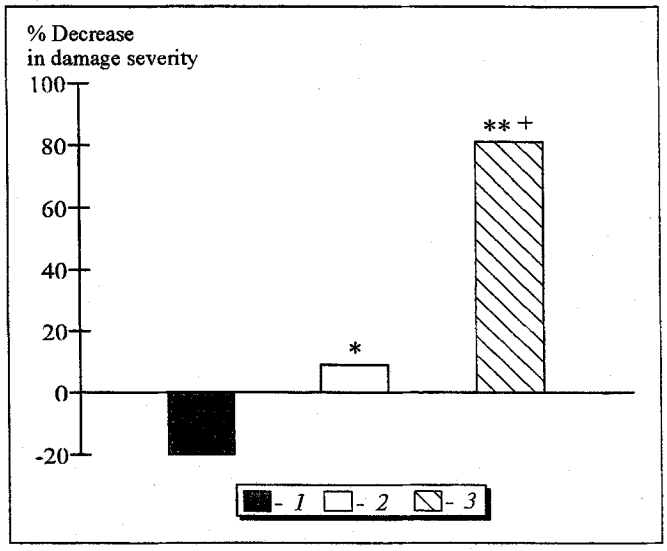

Fig. 3. Effects of OF-743 (10 mg/kg, *1*), OF-900 (10 mg/kg, 2), and their combination (3) on stress-induced peptic ulcer. *$p<0.05$, **$p<0.005$ compared with the control; +$p<0.005$ compared with OF-900. Negative values indicate increased ulcer severity in comparison with the control.

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Mechanism of Heart-Rate Acceleration Caused by Stimulation of Vagal Centers in the Frog

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The mechanism by which heart rate is increased upon stimulation of vagal centers is studied using frog heart preparations perfused with Ringer—Locke solution containing atropine and/or benzohexonium. Atropine stimulates vagus-induced heart-rate acceleration in dilutions of 10^{-6} and 10^{-5} g/ml. In a dilution of 10^{-4} g/ml both atropine and benzohexonium abolish vagal tachycardia. Rausedyl (3-4 injections, 5 mg/kg, at 18-20-h interval) prevents tachycardia. Stimulation of both halves of the medulla oblongata increases heart rate to a greater extent than stimulation of one half.

Key Words: *heart; regulation; vagus*

Stimulation of the vagus not only decreases but also increases heart rate [3,4,8-12]. Although the acceleration phenomenon was discovered in the 1850s, the controversy over its mechanisms still exists. In our view, only adrenergic and cholinergic hypotheses have gained sufficient experimental support. According to the adrenergic hypothesis, acceleration of heart rate is mediated by intracardiac adrenergic neurons forming synapses with preganglionic parasympathetic fibers of the vagus [3,4,11]. This hypothesis is supported by experiments in the vagal accelerating effect was abolished by sympatholytics [1,3] and ganglionic blocking agents [3], but not by atropine [1,12]. The adrenergic hypothesis is also consistent with the tentative presence of adrenergic neurons in the heart of various animal species [2].

The cholinergic hypothesis postulates that acceleration of cardiac rhythm upon vagal stimulation with a series of electric pulses is mediated by the same cholinergic neurons and, consequently, by the same neurotransmitter (acetylcholine): strong stimulation and high concentration of acetylcholine increase heart rate, while weak stimulation and low concentration of the neurotransmitter decrease it [5,6,8,9]. This hypothesis is supported by the absence of inhibitory and acceleratory effects in frogs with atropine-blocked M-cholinergic receptors [5, 6], preservation of vagal acceleratory effect in the presence of sympatholytics [5,6], and tentative absence of cardiac adrenergic neurons in some animal species.

Thus, on the one hand it was demonstrated that vagal acceleration of cardiac activity is prevented by blockade of the sympathetic nervous system and is not influenced by atropine that blocks the autonomic nervous system. On the other hand, there is evidence that atropine, but not sympatholytics, prevents vagal acceleration of heart rate.

Our goal was to analyze these results and to identify the neurotransmitter mediating vagal stimulation of cardiac activity in frogs.

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