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The Antioxidant Properties of Histamine Receptor Blockers: a Comparative Study in a Model System

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Antioxidant activities of seven histamine receptor blockers are compared using a model system of multilayer liposomes, chemiluminescence analysis, and 2-thiobarbituric acid-reactive substance assay. According to a decrease in the antioxidant activity, the drugs can be arranged as follows: diprazine, suprastin, tavegil, diazoline, dimedrol, phencarol, and ranitidine. The possible mechanisms of the antioxidant activity and the significance of the antioxidant properties of these drugs for experimental research and clinical practice are discussed.

Key Words: *antihistamines; antioxidant activity; chemiluminescence*

It has been generally accepted that the effects of antihistamine drugs result predominantly from the blockade of histamine receptors in the target tissues. However, these drugs display a broad spectrum of pharmacological activities. For example, some antihistamine preparations inhibit free-radical reactions [3,4]. Elucidation of the mechanisms responsible for the antioxidant activity of antihistamine drugs can be helpful in expanding the range of indications for these drugs, since the inhibitors of free-radical oxidation (FRO) are known to increase cell resistance to damaging factors by stabilizing plasma membranes. Consequently, antihistamines can be used for prevention and treatment of numerous diseases [2]. So far, the antioxidant properties of histamine receptor blockers have not been studied in detail. Our objective was to examine the antioxidant effects of several antihistamine drugs widely used in clinical practice.

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MATERIALS AND METHODS

The effects of diprazine, suprastin, diazoline, dimedrol (Russia), tavegil (clemastin, Egis), phencarol (Latvia), and ranitidine (Glaxo) were examined.

Free-radical oxidation was measured in a model system consisting of multilayer liposomes prepared from egg-yolk lipoproteins as described [3]. The intensity of FRO was assessed by the kinetics of Fe^{2+}-induced chemiluminescence (CL), and the concentration of thiobarbituric acid reactive substances (TBARS) was determined as described elsewhere [5]. Phosphate buffer (7.6 ml, 20 mM KH_2PO_4 and 105 mM KCl, pH 7.4), 1 ml eosin (2.7 mM), 0.3 ml egg-yolk lipoprotein suspension, and 0.1 ml ethanol solution of the test drug were successively added to the measuring cell so that the final concentration of the drug in the reaction mixture was 10^{-3}-10^{-7} M. After a 2-min incubation with continuous stirring, 1 ml $FeSO_4 \times 7H_2O$ (20 mM) was added to the cell, and the CL kinetics was recorded. To evaluate the antioxidant activity of the drugs, the tangent was cal-

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TABLE 1. Effects of Antihistamine Drugs on Fe^{2+}-induced CL in Liposome Suspension

Concentration, M		Rate of increase in slow CL burst (tgδ), % of the control
Diazoline	10^{-7}	97.3±10.7
	10^{-6}	93.0±12.1
	10^{-5}	96.0±8.8
	10^{-4}	94.0±8.6
	5×10^{-4}	32.0±6.2*
	10^{-3}	18.7±4.0*
Diprazine	10^{-7}	85.6±9.9
	10^{-6}	68.7±8.1*
	5×10^{-6}	35.1±5.8*
	10^{-5}	23.4±3.5*
	5×10^{-5}	0*
	10^{-4}	0*
Dimedrol	10^{-7}	103.2±13.6
	10^{-6}	108.6±12.8
	10^{-5}	95.8±10.9
	10^{-4}	91.7±10.7
	5×10^{-4}	86.4±11.2
Ranitidine	10^{-7}	102.8±8.1
	10^{-6}	103.5±8.6
	10^{-5}	99.4±7.2
	10^{-4}	97.0±8.5
	10^{-3}	94.3±6.9
Suprastin	10^{-7}	99.9±11.5
	10^{-6}	93.7±13.2
	10^{-5}	80.6±10.7
	10^{-4}	31.0±7.0*
	5×10^{-4}	4.7±1.3*
Tavegil	10^{-7}	96.5±10.6
	10^{-6}	86.1±9.4
	10^{-5}	74.6±7.9*
	10^{-4}	64.4±7.0*
	10^{-3}	36.5±5.8*
Phencarol	10^{-7}	101.7±10.0
	10^{-6}	98.4±12.3
	10^{-5}	100.9±12.8
	10^{-4}	95.8±9.6
	10^{-3}	99.1±10.4

Note. Here and in Table 2: *$p<0.05$ in compared with control samples.

culated for the slope of the exponential portion of the "slow" CL burst.

The concentration of TBARS and antioxidant activities of the drugs in a model system of multilayer liposomes from egg-yolk lipoproteins were determined by standard methods [3,5].

TABLE 2. Effects of Antihistamine Drugs on TBARS Concentration in Liposome Suspension

Concentration, M		TBARS content, % of control
Diazoline	10^{-7}	96.6±6.1
	10^{-6}	91.4±5.3
	10^{-5}	80.6±5.0*
	10^{-4}	70.3±4.3*
	10^{-3}	29.7±2.8*
Diprazine	10^{-7}	96.7±5.8
	10^{-6}	80.1±5.5*
	5×10^{-6}	52.0±3.6*
	10^{-5}	35.3±2.9*
	5×10^{-5}	19.4±1.5*
	10^{-4}	8.2±0.6*
Dimedrol	10^{-7}	94.1±6.2
	10^{-6}	97.2±4.8
	10^{-5}	84.1±5.0*
	10^{-4}	81.1±5.3*
	5×10^{-4}	79.9±4.6*
Ranitidine	10^{-7}	98.2±6.3
	10^{-6}	88.2±5.8
	10^{-5}	86.0±5.5
	10^{-4}	83.9±4.7*
	10^{-3}	70.8±3.8*
Suprastin	10^{-7}	94.4±6.2
	10^{-6}	88.4±6.4
	10^{-5}	84.9±5.9*
	10^{-4}	68.8±3.9*
	5×10^{-4}	44.8±2.2*
Tavegil	10^{-7}	98.5±7.2
	10^{-6}	93.7±6.6
	10^{-5}	90.9±6.9*
	10^{-4}	84.3±5.7*
	10^{-3}	40.8±3.1*
Phencarol	10^{-7}	100.8±5.9
	10^{-6}	97.0±5.5
	10^{-5}	98.2±4.7
	10^{-4}	101.4±5.9
	10^{-3}	96.9±4.1

The significance of differences was evaluated by the nonparametric Wilcoxon—Mann—Whitney U test.

RESULTS

The inhibitory effects of the antihistamine preparations on FRO varied considerably. The effect of phencarol on the intensity of Fe^{2+}-induced CL and

on the TBARS content in suspension of multilayer liposomes was the weakest (Tables 1 and 2). The H_1-receptor blocker dimedrol and the H_2-receptor antagonist ranitidine had no effect on CL, but at high concentrations (>10^{-5} M) slightly (15-30%) decreased the concentration of TBARS. Thus, phencarol, dimedrol, and ranitidine produced no appreciable effect on FRO *in vitro*.

Free-radical oxidation was not affected by relatively low concentrations (10^{-5}-10^{-7} M) of suprastin, diazoline, and tavegil. However, it was markedly inhibited by higher concentrations of these drugs with a parallel decrease in the intensity of the slow burst (tgδ) and in the accumulation of lipid peroxidation (LPO) products. At 10^{-4} M, tavegil and suprastin decreased tgδ by 1.6- and 3.2-fold, respectively (Table 1); the decrease in the concentration of TBARS was statistically significant, although less pronounced (Table 2). Diazoline exhibited antioxidant activity at higher concentrations (5×10^{-4}-10^{-3} M), while the relationship between the TBARS content and drug concentration was the same as with suprastin and tavegil.

Diprazine displayed the highest level of antioxidant activity. Micromolar concentrations of diprazine significantly decreased both tgδ and TBARS concentration (Tables 1 and 2), while at 5×10^{-5} M and higher it lowered these parameters to zero.

A comparative analysis showed that regardless of how much tgδ changed in response to antihistamine preparation, the intensity of the fast burst remained at the control level throughout the entire range of the drug concentrations.

Antioxidant activity calculated by the standard method was $4.0\pm0.28\times10^5$ M^{-1} for diprazine, $2.4\pm0.19\times10^4$ M^{-1} for suprastin, $3.2\pm0.23\times10^3$ M^{-1} for tavegil, and $2.8\pm0.20\times10^3$ M^{-1} for diazoline. We failed to calculate antioxidant activities for dimedrol, phencarol, and ranitidine as they were very low. It is reasonable to assume that the antioxidant activities of these drugs are close to zero.

Thus, the antihistamine drugs tested in this study can be divided into the following groups:

1) drugs with pronounced antioxidant activity (diprazine);

2) drugs with moderate antioxidant activity (suprastin, tavegil, and diazoline;

3) drugs with no antioxidant activity (dimedrol, phencarol, and ranitidine).

Our findings are consistent with the established ability of antihistamine preparations to inhibit FRO, as evidenced by lowered concentrations of free radicals in model cell-free lipid-containing systems and from decreased production of reactive oxygen species by blood phagocytes [4].

Only seven drugs were tested in this study, therefore, detailed pharmacochemical analysis and evaluation of the relationship between the antioxidant activity and the structure of these drugs were impossible. Nevertheless, since the ability of the H_1-receptor blockers to inhibit LPO reactions is similar to that of other compounds with analogous structure, it can be attributed to tertiary amino groups in close proximity to hexacyclic rings and/or to heterocyclic groups containing nitrogen atoms [1,4].

Since diprazine, suprastin, tavegil, and diazoline inhibit the slow burst of Fe^{2+}-induced CL and have no effect on the fast burst, it can be suggested that the antioxidant activity of these drugs is associated with their ability to act as free radical scavengers.

The discovery that H_1-receptor blockers exhibit different antioxidant activities may contribute to a better understanding of their molecular mechanisms of action, implying new fields for their use in experimental research and clinical practice.

REFERENCES

1. M. V. Bilenko, *Ischemia- and Reperfusion-Induce Damage to the Internal Organs* [in Russian], Moscow (1990).
2. Yu. A. Vladimirov, *Pat. Fiziol.*, No. 4, 7-19 (1989).
3. G. I. Klebanov, I. V. Babenkova, Yu. O. Teselkin, *et al.*, *Lab. Delo*, No. 5, 59-62 (1988).
4. R. D. Seifulla and I. G. Borisova, *Farmakol. Toksikol.*, **53**, No. 6, 3-10 (1990).
5. V. N. Syrov, Z. A. Khushbaktova, V. M. Gukasov, *et al.*, *Khim.-Farm. Zh.*, **21**, No. 1, 59-62 (1987).