EFFECTS OF ANTIHISTAMINES ON THE ACTION OF BRADYKININ

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Antihistamines, namely Dimedrol (diphenhydramine), Diprazin (Pipolphen), Tavegyl, and Suprastin, reduced the spasmogenic effects of bradykinin and the increased permeability of the microvessels caused by this polypeptide, in isolated segments of guinea pig ileum and also in rats and guinea pigs. The antibradykinin action of the antihistamines is nonspecific in character. No correlation was found between the chemical structure and intensity of the antibradykinin action of the various histamines tested.

KEY WORDS: antihistamines; bradykinin; smooth muscle; microvessels.

The role of histamine and bradykinin in the pathogenesis of inflammatory and allergic-anaphylatic reactions has been demonstrated by extensive experimental and clinical observations [1, 5, 10]. Both these endogenous biologically active substances possess some similar pharmacological properties: They cause increased permeability of the microvessels, lowering of the systemic arterial pressure, spasm of the muscles of internal organs, pain, and so on.

Information on the effects of antihistamines or the action of bradykinin is contradictory. Dimedrol (diphenhydramine) [2, 3, 6] and cyproheptadine [4] have been shown to possess nonspecific antibradykinin activity and there is evidence that mepyramine and other antihistamines do not possess activity of this type [7].

The object of the present investigation was to study the antibradykinin activity of Dimedrol and of other antihistamines – Tavegyl, Suprastin, and Diprazin (Pipolphen), members of chemically different classes (benzhydrol, phenothiazine, aminopyridine, and pyrrolidine). An attempt also was made to compare the antihistamine activity of these drugs with their effect on some actions of bradykinin.

EXPERIMENTAL METHOD

Dimedrol – hydrochloride of the β-dimethylaminoethyl ester of benzhydrol – was from the "Akrikhin" Pharmaceutical Chemical Factory, USSR; Diprazin (promethazine) – 10-(2-dimethylaminopropyl)-phenothiazine hydrochloride – was used under the name of Pipolphen, from EGYT, Hungary; Suprastin – N-dimethylaminoethyl-N-(p-chlorobenzyl)-aminopyridine – was from EGYT, Hungary; Tavegyl – 1-methyl-2-[2-α-methyl-p-chlorodiphenyl(methylhydroxy)-ethyl]-pyrrolidine hydrofumarate – was from EGYT, Hungary; Parmidine – bis-N-methylcarbaminic ester of 2,6-bishydroxymethylpyridine – was used under the name of pyridinol carbamate, from the All-Union Pharmaceutical Chemical Research Institute, USSR; histamine dihydrochloride was from L'vov Pharmaceutical Chemical Factory, USSR; bradykinin triacetate was from Reanal, Hungary.

The effect of the antihistamines on the spasmogenic effects of histamine and bradykinin was studied on isolated segments of the guinea pig ileum [8]. Contractions of the intestine were induced by histamine and bradykinin (1×10^{-7} - 1×10^{-8} g/ml). The presence and strength of action of the drugs was judged from the decrease in contraction of the ileum after preliminary (2-3 min beforehand) addition of aqueous solutions of the antihistamines to the vessel containing the organ. Intestinal tone was recorded under isotonic conditions by means of a balanced pen (ratio between the arms 1 : 7) on the smoked drum of a kymograph. The experimental results were subjected to statistical analysis: dose–effect curves were plotted and concentrations reducing the spasmogenic effect by 50% (EC_{50}) were calculated.

The effect of the antihistamines on edema of the paw caused by subplantar injection of histamine or bradykinin in a dose of 10 μg (0.1 ml of the 0.01% solution) was studied in noninbred male rats weighing 130-

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TABLE 1. Effect of Antihistamines on Spasmogenic Action of Histamine and Bradykinin

Antihistamine	EC_{50}, g/ml [1]		Minimal effective dose, mg/kg [2]	
	histamine	bradykinin	histamine	bradykinin
Dimedrol	$1 \cdot 10^{-9}$	$7 \cdot 10^{-7}$	0,05	0,1
Tavegyl	$1 \cdot 10^{-10}$	$8 \cdot 10^{-7}$	0,01	0,5
Diprazin	$3 \cdot 10^{-10}$	$8 \cdot 10^{-7}$	0,05	0,5
Suprastin	$1 \cdot 10^{-10}$	$5 \cdot 10^{-6}$	0,05	1,0
Parmidine	$1 \cdot 10^{-4}$	$5 \cdot 10^{-7}$	10,0	0,05

[1]Concentration of drug reducing spasmogenic effect of histamine or bradykinin by 50% in experiments on isolated segments of guinea pig ileum.

[2]Minimal effective dose in experiments with bronchospasm induced in guinea pigs.

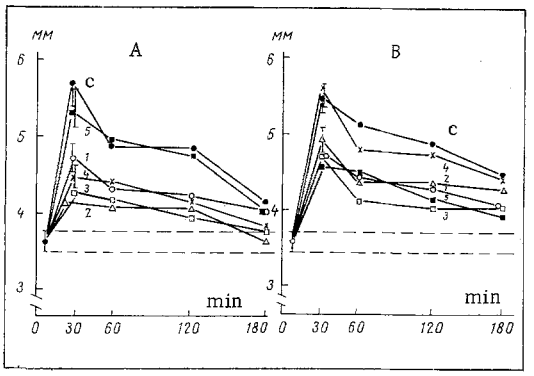

Fig. 1. Effect of Dimedrol (1), Tavegyl (2), Diprazin (3), Suprastin (4), and Parmidine (5) on edema of the limb produced in rats by histamine (A) and bradykinin (B). Each point on graph is mean of six measurements (M ±m). C) Control. Abscissa, time (in min); ordinate, diameter of paw (in mm).

150 g (n=70). The diameter of the hind paw was measured with calipers [13]. The drugs were injected intraperitoneally in doses of 12.5 and 25 mg/kg, 30 min before the histamine and bradykinin. The action of each dose of the antihistamines was studied on six animals.

The effect of the antihistamines on the bronchoconstrictor action of histamine and bradykinin was studied in guinea pigs of both sexes weighing 400-500 g, anesthetized with urethane (1.2 g/kg, intraperitoneally, when spontaneous respiration was blocked by intravenous injection of the curariform agent Diplacin in a dose of 30 mg/kg [11]. Bradykinin, histamine, and the antihistamines were injected through a catheter into the jugular vein as aqueous solutions in volumes of 0.2-0.3 ml.

In all the experiments Parmidine (pyridinol carbamate) was used as the standard antibradykinin preparation.

EXPERIMENTAL RESULTS

In experiments on isolated segments on the guinea pig ileum all the antihistamines reduced the spasmogenic effect of bradykinin, although their action was 2-10 times weaker than that of Parmidine. Dimedrol had the strongest antibradykinin action, followed in order of decreasing activity by: Tavegyl > Diprazin > Suprastin (Table 1).

Comparison of the antibradykinin activity of the drugs with their antihistamine action showed that all reduced the spasmogenic effect of histamine in concentrations 100-1000 times lower than in the experiments with bradykinin.

The antihistamines inhibited the increased permeability of the microvessels caused by bradykinin, reducing edema of the limb by 20-40% depending on the dose (Fig. 1B). Suprastin was the exception in these ex-

periments, for in the highest dose used (25 mg/kg) it had no appreciable effect on bradykinin edema. In the strength of their action the other antihistamines were similar to one another and also to Parmidine. In parallel experiments with histamine, Parmidine in a dose of 50 mg/kg had no effect on the development of edema, whereas the antihistamines reduced it by 30-60% depending on the dose. The most marked inhibition of histamine edema was caused by Tavegyl and Diphazin; Suprastin and Dimedrol had a weaker action (Fig. 1A).

In the experiments on guinea pigs, all the antihistamines inhibited the development of bradykinin bronchospasm. Their action was dose-dependent in character and lasted 120-240 min. Dimedrol was most active in this respect; the other antihistamines did not differ significantly from one another in the strength of their action. Comparative experiments showed that Parmidine was only twice as active as the antihistamines in its effect on bradykinin-induced spasm of the bronchial muscles, whereas in the experiments with histamine, the action of the drugs was 1000 times stronger or more than that of Parmidine (Table 1).

The results indicate that antihistamines belonging to different chemical groups possess nonspecific antibradykinin activity and reduce or prevent (depending on the dose and the test used) the effects of bradykinin. Since there are features of similarity in the structure of kinin receptors and choline receptors [9, 12] it can be postulated that the antibradykinin activity of individual antihistamines is linked with their cholinolytic properties.

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