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BROMPHENIRAMINE AND THE CARDIO-VASCULAR EFFECTS OF NOREPHEDRINE AND NORADRENALINE

By

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Brompheniramine (BPH) is a potent antihistaminic drug with only little sedative effects (4). Similar to some other antihistamines of various chemical structures, BPH may prevent the uptake of noradrenaline into isolated adrenergically innervated tissues (8, 9, 2). The significance of this effect of antihistamines is not known, but animal experiments have demonstrated that antihistaminic agents can potentiate the cardiovascular effects of noradrenaline and adrenaline (16, 8, 9, 11).

Similar to ephedrine, norephedrine (NEPH) is a sympathomimetic drug that, in combination with antihistamines, is used orally as nasal decongestants (7). In this combination, it is the α -adrenoceptor mediated vascular constriction that adds to the antihistaminic effect. NEPH seems to differ from ephedrine in two respects: it is a less fat molecule with less tendency to produce CNS effects (7), and it may be a more directly-acting sympathomimetic drug than ephedrine (19, 20).

BPH and NEPH are common active ingredients in oral decongestant preparations (13, 14). As BPH might influence the effect of sympathomimetic amines, possibly by inhibition of the neuronal uptake mechanism, we studied the effect of

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BPH on the cardiovascular actions of NEPH and noradrenaline in anaesthetized cats. In addition, interaction experiments and studies of the direct sympathomimetic effect of NEPH were performed on isolated rabbit aorta preparations.

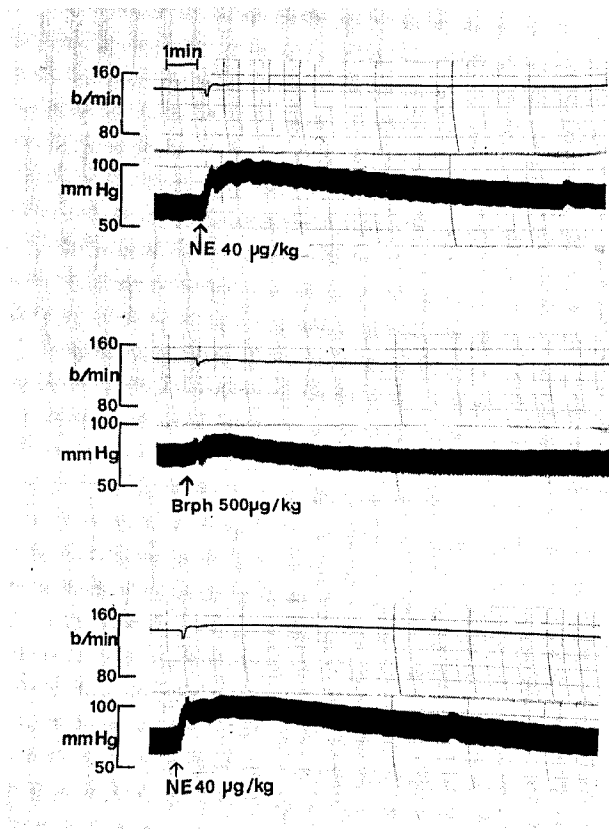


Fig. 1.

The effects of norephedrine (NE) and brompheniramine (Brph) on heart rate (upper traces, beats/min) and carotid blood pressure (lower traces, mm Hg). Brph was given between the two doses of NE. In this dose Brph only causes a slight effect on heart rate and blood pressure and does not change the effects of NE.

METHOD

Cardiovascular Experiments in vivo

Adult cats (2.5–3.5 kg) of both sexes were anaesthetized by i.p. injection of 40 mg/kg pentobarbital sodium (Abbott) and placed on a thermostated operation table, which kept the rectal temperature at approximately 38° C. Additional pentobarbital was given slowly i.v. (left femoral vein, 30 mg/h) by means of an infusion pump (Braun). The trachea was cannulated and the animals received artificial respiration. The arterial blood pressure was measured through the left carotid artery connected to a pressure transducer (Statham P23AC). Heart rate was recorded by a tachometer triggered by the ECG. The drugs were injected i.v. in the v. cava via a catheter inserted through the right femoral vein. All recordings were made on a Grass polygraph (7P1).

Antihistaminic Potency of Brompheniramine (BPH) in vivo

Adult cats of both sexes weighing 2.5–3.5 kg were used. They were prepared according to the blood pressure experiment, respiratory overflow being measured by the method of Konzett & Rössler (12). Bronchoconstriction was produced in two ways:

1. Injection of histamine 1–5 µg/kg i.v.
2. Inhalation of an aerosol containing 0.15–0.3 mg/ml histamine dissolved in a water solution of 10 per cent glycerol (15).

BPH was given i.v. The antihistaminic potency was evaluated when the histamine-induced bronchoconstriction, by repeated i.v. and aerosol administrations, was reproducible.

Isolated Rabbit Aorta Strips

Rabbit aorta strips were prepared according to "Pharmacological Experiments on isolated preparations" (E. and S. Livingstone Ltd. Edinburgh and London 1968). Some rabbits were treated with reserpine (5 mg/kg) i.p. or i.v. 16 hours before the aorta was excised. The preparations were mounted in organ baths containing Krebs' solution 37° C and bubbled with carbogen. Isometric tension changes were recorded by means of a strain-gauge transducer on a Grass Polygraph (7P1). Initial tension was approximately 3 g. The strips were left to stabilize in the bath for 1 h before the experiment started. Drugs in volumes less than 1 ml were added to the bathing solution.

Drugs: Histamine chloride, dl-brompheniramine maleate, l-noradrenaline tartrate, ± norephedrine chloride, cocaine chloride, and reserpine. The drugs were dissolved in physiological saline before each experiment. Noradrenaline solutions were stabilized with ascorbic acid 0.2 mg/ml and kept cold during the experiments.

TABLE
Blood Pressure (Systolic,

Exp.	Dose μg/kg	Control			Brph 100 μg/kg		
		Before	Max. effect	Diff.	Before	Max. effect	Diff.
1.	10	110	122	12	124	138	14
27/11-72	20	120	145	25	114	147	33
	40	112	145	33	117	154	37
2.	10	116	127	11	107	122	15
28/11-72	20	104	129	25	105	131	26
3.	10	85	93	8			
29/11-72	20	95	108	13			
	40	95	114	19	95	117	22
4.	10	99	114	15	105	118	13
30/11-72	20	96	122	26	97	122	25
5.							
1/12-72	50	82	123	41	85	126	41
6.							
4/12-72	50	70	140	70	70	130	60
7.	50	135	185	50	140	175	35
6/12-72	200	150	270	120	145	238	93
8.	10	80	92	12			
13/12-72	25	83	103	20			
	50	88	125	37	105	137	32
9.	20	80	117	37			
18/12-72	40	74	120	46	75	112	37

The table shows the effects of norephedrine (NE) on the systolic blood pressure (mm each cat. The "Before" column represents the systolic blood pressure just before the

RESULTS

Cardiovascular Effect in vivo

The basal systolic arterial blood pressure (ABP) varied between 63-107 mm Hg in the cats. The range for basal heart rates was 140-176 beats/min. Higher doses of BPH

1
mm Hg) Norephedrine.

Brph 500 µg/kg			Brph 1000 µg/kg			Brph 5000 µg/kg		
Before	Max. effect	Diff.	Before	Max. effect	Diff.	Before	Max. effect	Diff.
120	132	12	124	130	6			
123	148	25						
111	131	20	106	109	3	102	106	4
108	139	31				100	110	10
92	105	13	100	111	11	95	101	6
100	120	20	100	120	20	100	120	20
80	126	46	87	116	29	69	84	15
135	208	73						
107	128	22						
87	110	23	77	100	23			

Hg) in 9 cats. Control figures represent mean values from at least two evaluations in injection of NE. Brompheniramine was given 10-15 min before NE.

(≥ 1 mg/kg but not lower doses, cf. Fig. 1) caused a lasting depressor effect. Before the high doses were given, the basal arterial blood pressure for each cat changed less than 10 mm Hg during the course of the experiment. Under the same conditions, the heart rate changed less than 20 beats/min.

Dose-response with NEPH and noradrenaline was ob-

tained in all cats. NEPH was regularly given in doses below 100 $\mu\text{g}/\text{kg}$. Within this dose range, NEPH consistently produced reproducible dose-related responses. The blood pressure was also sensitive to further increases in NEPH dosage, as shown in two cats that received 200 $\mu\text{g}/\text{kg}$. Below 100 $\mu\text{g}/\text{kg}$ of NEPH, an interval of 30 min between injections proved suitable. Then a given dose of NEPH produced the same degree of effect during the experimental period. Consistent responses to noradrenaline below 1 $\mu\text{g}/\text{kg}$ were recorded with a dosing interval of 5–10 min. These low doses of the amines that produced responses of similar magnitude were used partly because of the greater possibility of repeating the effect evaluation in one animal and partly because of the necessity of using low doses of adrenergic amines in experiments on uptake interaction, as pointed out by Iversen (10).

Administration of NEPH did not affect the responses to subsequent doses of noradrenaline within the dose ranges used. This was considered important because previous investigations had revealed that ephedrine might potentiate effects of subsequent doses of noradrenaline (6). Actually, in one case, the effect of noradrenaline after 200 $\mu\text{g}/\text{kg}$ of NEPH was slightly increased compared with control value, but this was not seen with the lower doses regularly used in the study.

Interaction of the monoamines was evaluated within 15 min after brompheniramine was given. Brompheniramine up to 500 $\mu\text{g}/\text{kg}$ (10, 100, 500 $\mu\text{g}/\text{kg}$) did not change the pressor response to norephedrine (Table 1, Fig. 1). Higher doses (≥ 1000 $\mu\text{g}/\text{kg}$) of brompheniramine counteracted the effect of norephedrine on arterial blood pressure (Table 1). No consistent effect of various doses of brompheniramine was seen on the response to noradrenaline (Fig. 2).

Brompheniramine up to 500 $\mu\text{g}/\text{kg}$ did not affect the heart rate responses to the two amines. Larger doses of brompheniramine depressed the effects of noradrenaline and NEPH on the heart rate (Table 2, Figs. 1, 2). In 4 cats, cocaine 1–5 mg/kg potentiated the effects of noradrenaline on heart rate

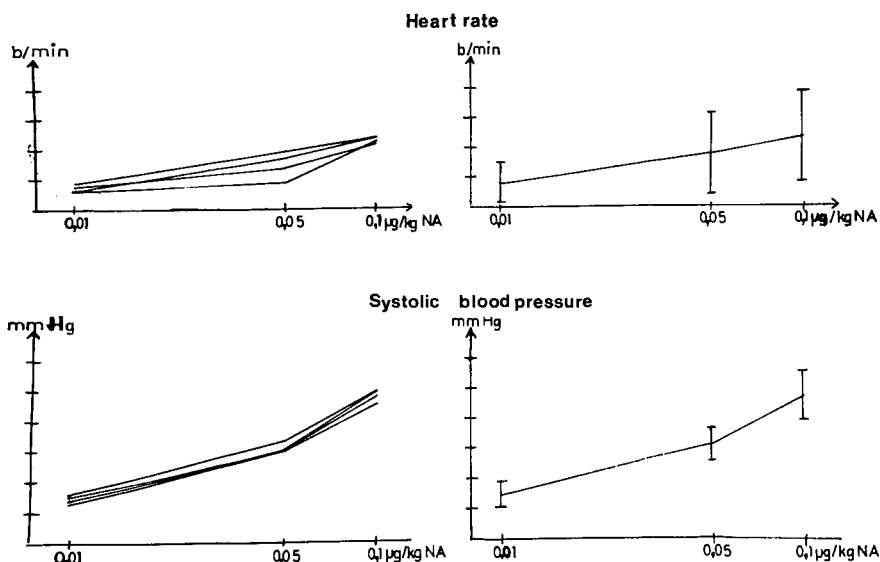


Fig. 2.

The effects of noradrenaline (NA) on heart rate and arterial systolic blood pressure in 9 cats. The curves on the left part of the figure show the mean dose response of control doses of NA and of NA given after brompheniramine 100, 500 and 1000 $\mu\text{g/kg}$. These four curves did not show any consistent difference. The right part of the figure illustrates the mean values of all the effects of NA, irrespective of brompheniramine pretreatment. Vertical lines show the standard deviations.

and on arterial blood pressure. Neither of these effects were seen with brompheniramine.

Antihistaminic Potency in vivo

Threshold antihistaminic activity of BPH was produced by approximately 10 $\mu\text{g/kg}$, and a dose of 100 $\mu\text{g/kg}$ blocked the histamine effects, as shown in Fig. 3. The effects were consistently recorded in all experiments (4 cats). This response (dose 100 $\mu\text{g/kg}$) lasted approximately 1 h. The blood pressure decrease produced by histamine was only partly counteracted by BPH even when larger doses of BPH were given.

TABLE
Heart Rate (Beats/

Exp.	Dose μg/kg	Control			Brph 100 μg/kg		
		Before	Max. effect	Diff.	Before	Max. effect	Diff.
1.	10	150	155	5			
27/11-72	20	150	160	10			
	40	150	168	18	160	175	15
2.	10	168	180	12	139	145	6
28/11-72	20	161	179	18	144	160	14
3.	10	155	162	7			
29/11-72	20	149	163	14			
	40	145	165	20	144	159	15
4.	10	160	165	5	162	165	3
30/11-72	20	160	170	10	162	172	10
5.							
1/12-72	50	150	170	20	155	165	10
6.							
4/12-72	50	178	190	12	178	190	12
7.	50	150	165	15	148	160	12
6/12-72	200	132	190	58	150	190	40
8.	10	151	154	3			
13/12-72	25	144	149	5			
	50	142	150	8	151	157	6
9.	20	153	164	11			
18/12-72	40	148	164	16	141	159	18

The table shows the effects of norephedrine (NE) on the heart rate (beats/min) in The "Before" column represents the heart rate just before injection of norephedrine.

Isolated Aorta Experiments

Effects of BPH were evaluated on the contractions induced by NEPH and noradrenaline in isolated aorta strips (12 preparations from 3 rabbits). Threshold and maximum contractile effects were produced by NEPH 0.4-80 μg/ml and noradrenaline within the dose range 0.005-1.6 μg/ml. In

²
Min) Norephedrine.

Brph 500 µg/kg			Brph 1000 µg/kg			Brph 5000 µg/kg		
Before	Max. effect	Diff.	Before	Max. effect	Diff.	Before	Max. effect	Diff.
139	143	4	139	141	2	128	130	2
140	151	11				131	136	5
140	150	10	135	145	10	130	138	8
162	175	13	165	175	10	150	160	10
155	168	13	150	160	10	132	135	3
168	198	30						
151	156	5						
140	149	9	134	141	7			

9 cats. Control figures represent mean values from at least two evaluations in each cat.
Brompheniramine maleate (Brph) was injected 10-15 min before NE.

doses up to 0.8 µg/ml the presence of BPH in the bath had no effect on the contractions of submaximum doses of noradrenaline and NEPH. Higher doses of BPH depressed the contractions (see Fig. 4). These larger doses of BPH also depressed contractions of the aorta strips produced by carbacholine.

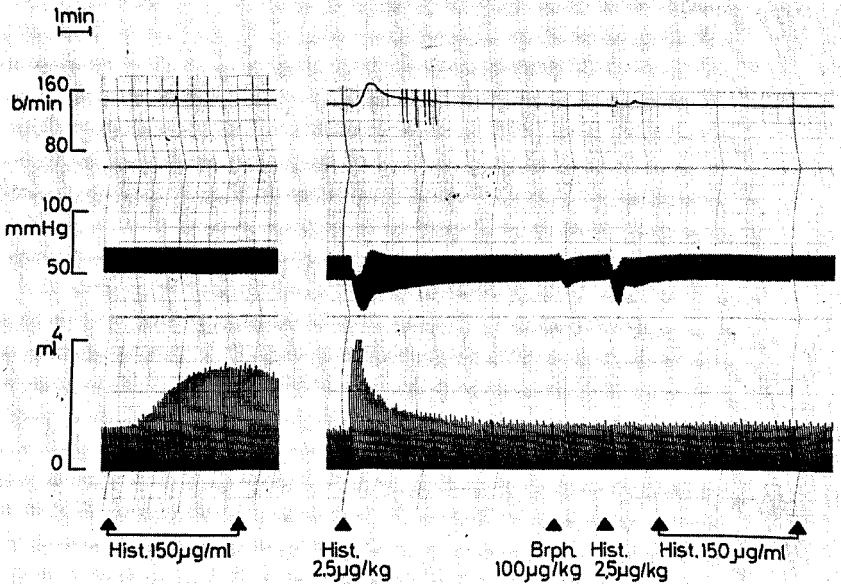


Fig. 3.

The effect of brompheniramine (Brph) 100 $\mu\text{g/kg}$ on histamine-induced bronchospasm. (Inhalation of an aerosol containing 150 $\mu\text{g/ml}$ histamine and i.v. injection of histamine 2.5 $\mu\text{g/kg}$). Heart rate (upper trace), carotid blood pressure (middle trace) and respiratory overflow (lower trace). Brph inhibits the induced bronchospasm caused by inhaled respectively i.v. histamine.

In preparations from three normal and three reserpine-treated animals dose-response curves to NEPH, added in cumulative doses to the bath, were evaluated. The results (Fig. 5) do not reveal any decrease of the norephedrine-induced effect in the reserpine-treated strips compared to normal strips.

DISCUSSION

The present results suggest that BPH, even in doses considerably larger than needed for antihistaminic activity, does not

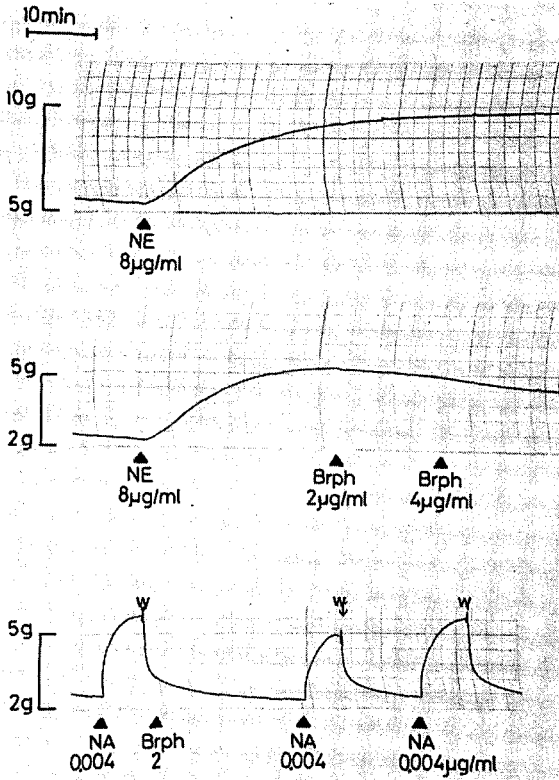


Fig. 4.

The effect of norephedrine (NE) and noradrenaline (NA) on isolated rabbit aorta strip. Upper trace: control contraction of NEE. Middle trace: Brph counteracts the NE contraction. Lower trace: Pretreatment with Brph depresses the contractile effect of NA.

interact with cardiovascular effects of noradrenaline and NEPH.

Carlsson & Lindquist (2) showed that BPH blocked the neuronal monoamine uptake *in vitro*. The effect of BPH on monoamine uptake, however, might not be present together with its antihistaminic effect, as approximately 1/100 of the

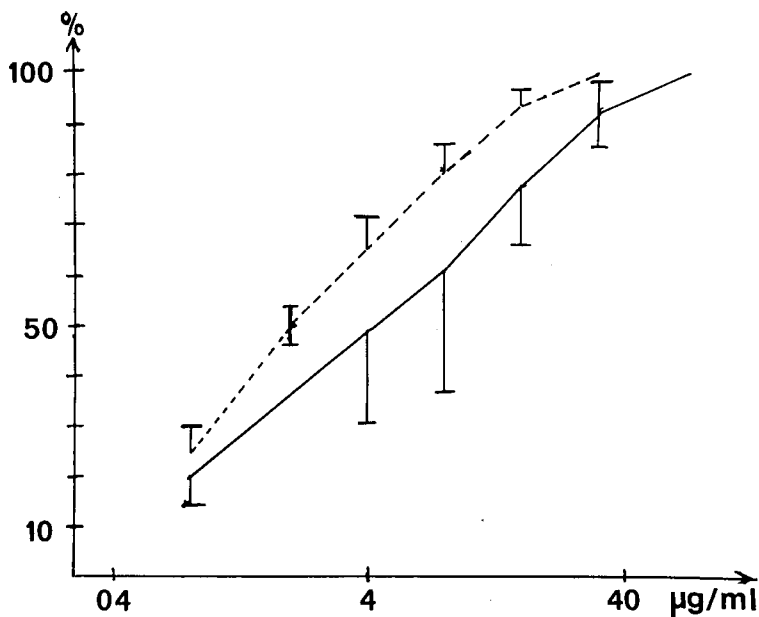


Fig. 5.

Cumulative dose response curves of norephedrine (NE) on isolated rabbit aorta from normal (—) and reserpine treated (---) rabbits. Each curve represents mean values from 6 preparations from 3 rabbits. Vertical lines show the standard deviations.

concentrations used by Carlsson & Lindquist (2) showed marked antihistamine effects in isolated smooth muscle preparations (17). A dosage difference between effect on uptake and antihistaminic activity agrees with the observations by Innes (5), who found that the potentiating activity of antihistamines on the effects of noradrenaline was unrelated to their antihistaminic potency.

The specific antihistaminic potency of BPH *in vivo* was evaluated on histamine-induced bronchoconstriction. This should be a more suitable parameter than the blood pressure, as the depressor effect by histamine is known to be partly resistant to antihistamines (11). In doses approximately 10 times those needed for marked antihistaminic activity *in vivo*,

BPH usually counteracted the cardiovascular effects of NEPH, but did not change the responses to noradrenaline. It seems unlikely that this effect of BPH is due to block of monoamine uptake because: a) inhibition of the physiological effects by block of uptake would mean that NEPH is mainly acting indirectly, which does not seem to be the case (see below); b) any blocking of uptake into neurons by BPH was insufficient to potentiate the effects of noradrenaline; c) *in vitro* experiments by Carlsson & Waldeck (3) and Ross *et al.* (18) suggest that NEPH has a low affinity to the membranal uptake mechanism of neurons. Then the unspecific depressive effect by BPH in high concentrations, as seen on the isolated aorta strips, could be responsible for the inhibitory effect on the NEPH induced responses *in vivo*.

Also another antihistamine drug, phenindamine, which is effective as a blocker of noradrenaline uptake (2, 8), was shown to be devoid of the cocaine-like potentiating effect on physiological responses to the adrenergic amine (9, 16).

The expected effect when a sympathomimetic amine interacts with uptake-blocking drugs is dependent on the mechanism of action of the amine; whether it produces direct, indirect, or mixed direct and indirect sympathomimetic effects. It is generally agreed that noradrenaline is a directly-acting sympathomimetic agent. Also NEPH seems to belong to the mainly directly-acting agents. Trendelenburg *et al.* (19, 20) showed that the dose-response curves for the effect of NEPH on nictitating membrane in cats were unaffected by treatment with reserpine, cocaine, and reserpine plus cocaine. Thus NEPH differed from ephedrine, which showed mixed direct and indirect actions. Also the blood pressure increase by NEPH was not significantly changed by reserpine treatment. This observation agrees with the present finding that the contractile potency of NEPH on aorta strips was not decreased in preparations prepared from rabbits pretreated with reserpine in doses known to deplete neuronal stores of adrenergic amines.

SUMMARY

Earlier reports have shown that antihistamines may potentiate physiological effects of adrenergic amines, possibly by interfering with the membranal uptake mechanism of neurons. The influence of i.v. brompheniramine (100–5000 $\mu\text{g/kg}$) on the cardiovascular effects of i.v. noradrenaline (0.1–1 $\mu\text{g/kg}$) and norephedrine (10–100 $\mu\text{g/kg}$) was studied in the anesthetized cat. In these *in vivo* studies, no interaction effect was recorded that could be due to block of uptake of monoamines by the antihistamine. On isolated rabbit aorta strips, it was shown that the contractile effect of norephedrine is probably a direct effect and that brompheniramine in antihistaminic doses did not change the effects of noradrenaline and norephedrine. High doses of the antihistamine were unspecifically depressive on the aorta strips. Perhaps a similar depressive effect can explain the finding that large doses of brompheniramine (≥ 1000 $\mu\text{g/kg}$) depressed the cardiovascular effects of norephedrine *in vivo*. Separate experiments on cats showed that brompheniramine specifically counteracted histamine-induced bronchoconstriction in doses 10–100 $\mu\text{g/kg}$. The present data suggest that in antihistaminic doses brompheniramine does not interfere with the cardiovascular effects of noradrenaline and norephedrine.

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