INHIBITORY ACTION OF OXYFEDRINE ON THE DEVELOPMENT OF ANAPHYLAXIS IN EXPERIMENTAL ANIMALS

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Many recent investigations have yielded evidence of a functional blockade of β-adrenoreceptors in patients with bronchial asthma [1]. It is evident that this is responsible for the particular urgency of the discovery of drugs to correct these changes.

In this connection the writers' attention has been drawn to the new drug oxyfedrine [L-3-(β-hydroxy-α-methyl-phenylethylamino)-3'-methoxypropiophenone hydrochloride]. Preliminary studies [5] have shown that oxyfedrine has a positive inotropic and bathmotropic action on the heart through its marked stimulating effect on coronary β-adrenoreceptors. Oxyfedrine has also been found to stimulate β-adrenoreceptors in the smooth muscles of animals, relaxing their tone [4].

From what has been said it can be suggested that oxyfedrine may have an antianaphylactic action. In this connection it was decided to analyze its possible use in allergologic practice, and the investigation described below was carried out for this purpose.

EXPERIMENTAL METHOD

Guinea pigs of both sexes weighing 250-300 g were sensitized with crystalline ovalbumin mixed with Freund's complete adjuvant by the method described previously [2]. The experiments were begun 3-4 weeks after the sensitizing injection. The inhibitory action of oxyfedrine on development of anaphylaxis in the animals was studied *in vivo* as reflected in the character of respiration and also on isolated segments of guinea pig small intestine.

The anaphylactic reaction *in vivo* was produced by an intravenous reacting injection of 1 mg ovalbumin [1].

Oxyfedrine, in the corresponding dose, was injected intravenously at different times in a volume of 0.1 ml before the reacting injection of antigen. Respiration of the animals was recorded by means of a Marey's capsule through the P-42 plethysmograph.

To produce an anaphylactic reaction in the isolated intestine, guinea pigs were exsanguinated by division of the carotid arteries and jugular veins. After bleeding, a portion of the ileum located nearest to the ileocecal angle was isolated, freed from mesentery, and a segment of intestine 1.5-2.0 cm long was excised. The segment was washed to remove intestinal contents and placed in a special bath for isolated organs (capacity 20 ml) at 37°C. Krebs' solution was used as the nutrient fluid [2].

Just as in the experiments *in vivo*, to produce an anaphylactic reaction of the segments of guinea pig intestine, thrice recrystallized ovalbumin in a dose of 100 μg/ml was used. The final concentration of the substances used in the bath for isolated organs is shown in this paper. Full details of the technique were described previously [2].

Oxyfedrine was used in the form of Ildamen.

EXPERIMENTAL RESULTS

In concentrations of between 390 and 1300 μg/100 g body weight oxyfedrine itself caused an increase in ventilation of the lungs of the intact guinea pigs, which depended on dose.

Preliminary injection of oxyfedrine into sensitized animals (40 experiments) also was accompanied by an increase in the intensity of respiratory movements. In experiments *in vivo*

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TABLE 1. Inhibitory Action of Oxyfedrine on Development of Anaphylactic Bronchospasm in Guinea Pigs *in vivo*

No. of experiments	Dose of oxyfedrine, μg/100 g body weight	Severity of anaphylactic bronchospasm		
		complete	partial	absent
14	0 (Control)	12	2	—
3	260—520	3	—	—
3	560—780	1	2	—
6	800—1000	—	3	3
14	1200	—	—	14

TABLE 2. Effect of Oxyfedrine on Response of Smooth Muscles to Specific Antigen and Histamine (M ± m)

Number of experiments	Concentration of oxyfedrine, μg/ml	Magnitude of anaphylactic reaction, %	Magnitude of reaction of standard dose of histamine, %
15	0 Control	95,5±4,8	100
6	10	73,3±7,8	96,6±4,8
6	20	28,2±2,3	85,5±6,1
6	30	18,3±0,9	74,0±2,2
12	40	0	55,1±3,1

preliminary injection of oxyfedrine in doses of 260-520 μg did not abolish the anaphylactic bronchospasm in guinea pigs sensitized with ovalbumin, but in this case its onset was considerably delayed. Intravenous injection of oxyfedrine in doses of 560-780 μg prevented death of the animal but did not completely abolish the bronchospasm. Preliminary injection of oxyfedrine in doses of 800-1000 μg partially, and in some cases completely, prevented the development of anaphylactic bronchospasm. However, the maximal effect of inhibition of anaphylaxis in guinea pigs by oxyfedrine was observed in a dose of 1200 μg (14 experiments). In that case the drug, injected intravenously, completely inhibited the development of anaphylactic bronchospasm, and all the animals of this series survived.

The results thus demonstrated a distinct and dose-dependent inhibition of anaphylactic bronchospasm in guinea pigs after injection of oxyfedrine in doses of 260 to 1200 μg/100 g body weight (Table 1).

In the concentrations tested, oxyfedrine did not completely prevent the development of histamine bronchospasm due to intravenous injection of histamine in a dose of 78 μg/100 g body weight. Tests of the action of oxyfedrine on anaphylaxis of smooth muscles showed that the drug preserved its antianaphylactic activity *in vitro* also. In this case the action of oxyfedrine in concentrations of 10-40 μg/ml was manifested by dose-dependent inhibition of the reaction of the animals' smooth muscles, assessed as the degree of contraction of segments of small intestine to a standard dose of histamine (2.5×10^{-7} M).

Preliminary perfusion of segments of intestine of sensitized guinea pigs with oxyfedrine in a concentration of 40 μg/ml (12 experiments) was accompanied by complete suppression of anaphylactic contraction of the smooth-muscle preparation (Table 2).

It was also shown that oxyfedrine, in the concentrations tested, caused distinct inhibition of the reaction of the smooth muscles to a standard dose of histamine (Table 2).

The antianaphylactic action of oxyfedrine, revealed by these experiments, is most probably associated with an increase in the cyclic AMP level in the smooth-muscle cells [1, 5]. As confirmation of this, it was shown that oxyfedrine, in a dose of 1200 μg/100 g body weight, which produced almost total inhibition of the anaphylactic reaction in guinea pigs, led to a marked rise in the cyclic AMP level (up to 0.96 ± 0.20 nmole/g lung tissue and up to 1.53 ± 0.16 nmole/g small intestine tissue) from initial levels of cyclic AMP in these tissues of 0.45 ± 0.11 and 0.65 ± 0.21 nmole/g respectively.

The antianaphylactic action of oxyfedrine *in vivo* and *in vitro* and its ability to induce a marked increase in cyclic AMP concentration thus suggest that the further study of the properties of this cardiotropic drug would be worthwhile with a view to its possible use to suppress some manifestations of allergy in man.

LITERATURE CITED

1. A. D. Ado, General Allergology [in Russian], Moscow (1978).
2. G. V. Poryadin, "Passive sensitization of human smooth-muscle organs," Author's Abstract of Candidate's Dissertation, Moscow (1969).
3. G. V. Poryadin and A. P. Baranov, Byull. Éksp. Biol. Med., No. 3, 76 (1975).
4. G. Pöch and W. Kukovetz, in: Action of Oxyfedrine, pp. 147-151.