SUPPRESSION OF THE ANAPHYLACTIC REACTION OF ISOLATED SMOOTH-MUSCLE ORGANS BY POTASSIUM ARSENITE

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The possibility of suppressing the anaphylactic reaction of human and guinea pig smooth muscle by means of inorganic arsenic was studied. Potassium arsenite (in the form of Fowler's solution) inhibited the development of anaphylactic contraction of human smooth muscle (ileum). Potassium arsenite completely blocked the development of anaphylactic bronchospasm and the liberation of biologically active substances from the lungs of guinea pigs.

KEY WORDS: *anaphylactic reaction; isolated smooth-muscle organs; potassium arsenite.*

Anaphylactic contraction of smooth muscle is the leading process in the pathogenesis of such threatening manifestations of allergy as bronchial asthma and anaphylactic shock. An important problem in this connection is the pharmacological control of this reaction.

Most antiallergic preparations nowadays used in clinical medicine act mainly on the liberation of a particular biologically active substance, thereby preventing its action on excitable cells. It can thus be understood that they can only reduce the degree of manifestation of the anaphylactic reaction. Hence the interest in the search for and study of substances with a broad spectrum of antagonistic action against biologically active substances without, at the same time, disturbing the general excitability of the smooth-muscle cell. Virtually no such substances are yet available.

Recently information has been published on the antianaphylactic action of inorganic arsenic preparations [7]. In the investigation described below the antianaphylactic action of potassium arsenite was studied on a model of anaphylaxis of isolated smooth-muscle organs of man and experimental animals.

EXPERIMENTAL METHOD

The possibility of suppressing the anaphylactic reaction of isolated smooth-muscle organs by inorganic arsenic (in the form of Fowler's solution) was studied on strips (measuring 0.5 × 1.5 cm) of human ileum removed from the region of healthy tissue during operations for abdominal tumors. For passive sensitization of segments of the intestine blood serum of untreated patients sensitive to ragweed pollen was used. Passive sensitization was carried out with human smooth-muscle organs by the method described previously [4, 6] and also in a model of active anaphylaxis of isolated smooth-muscle organs of guinea pigs (an isolated bronchus–lung preparation, or ileum), sensitized with crystalline ovalbumin mixed with Freund's complete adjuvant. Experiments were carried out on 27 male guinea pigs weighing 250-300 g. At the end of the period of sensitization (on the 21st day) the guinea pigs were exsanguinated by division of the carotid arteries and jugular veins. The bronchus–lung preparation and segments of the small intestine were removed. The lung preparation was placed in a special plastic chamber. Krebs's solution with dextran was used as the nutrient medium. Respiration was recorded by a Marey's capsule through the P-42 plethysmograph. Details of the method were described previously [1].

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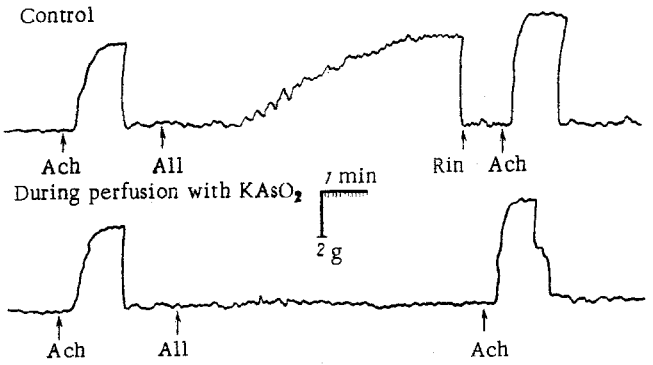

Fig. 1. Suppression of anaphylactic contraction of isolated segment of human ileum by potassium arsenite. ACh) Reaction of muscle to acetylcholine (2 μg/ml); All) reaction of muscle to specific allergen (extract of ragweed pollen, 30 μg/ml as nitrogen); Rin) rinsing organ with Krebs's solution for 10 min.

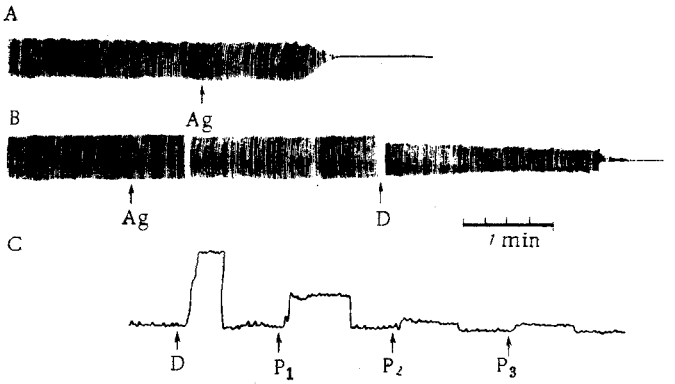

Fig. 2. Suppression of anaphylactic bronchospasm and liberation of biologically active substances from perfused lungs by potassium arsenite. A) Reproduction of anaphylactic bronchospasm; B) respiration during perfusion of lungs with potassium arsenite; C) control of liberation of biologically active substances from intestine of intact guinea pig; D) reaction of muscle to histamine (0.1 μg/ml); Ag) addition of specific antigen (ovalbumin, 200 μg/ml); P_1) perfusion fluid of lungs after anaphylactic bronchospasm; P_2) perfusion fluid of lungs of intact animal (control); P_3) perfusion fluid of lungs after addition of specific antigen and perfusion with potassium arsenite.

The anaphylactic reaction of segments of the human and guinea pig ileum was reproduced in a bath for isolated organs with a volume of 20 ml at a temperature of 37°C. Krebs's solution was used as the nutrient medium.

To produce the anaphylactic reaction of the intestine of a person sensitized with reaginic serum from patients sensitive to ragweed, an extract of ragweed pollen in a concentration of 30 μg/ml (as nitrogen), made up in phosphate buffer, pH 7.0, was used. To produce the anaphylactic reaction of the intestine and anaphylactic bronchospasm of the bronchus–lung preparation from guinea pigs sensitized with ovalbumin, ovalbumin recrystallized 3 times was used in a dose of 100 μg/ml. The final concentration of the test substances in the bath for isolated organs is indicated in this paper. Incubation of the tissues in a solution of ^{131}I-labeled immunoglobulin was carried out in the same way as passive sensitization [4]. The numerical results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

The magnitude of the anaphylactic contraction of the segments of human ileum, sensitized passively with the sera of patients with pollinoses, expressed as a percentage of their reaction to a standard dose of acetylcholine (2.0 μg/ml), was 71.1 ± 2.2% in nine experiments.

Preliminary perfusion with potassium arsenite in a concentration of 200 μg/ml for 20 min completely suppressed anaphylactic contraction of the segments of human ileum in all 10 experiments of this series (Fig. 1). The sensitivity of the smooth muscle to acetylcholine was unchanged. The reaction of strips of ileum to acetylcholine during perfusion with Krebs's solution with the addition of Fowler's solution amounted in nine experiments to 94.1 ± 9.0% of the control.

The action of arsenic preparations also was studied on the anaphylactic reaction of isolated smooth-muscle organs (intestine and bronchus–lung preparation) of guinea pigs sensitized actively to ovalbumin. In control experiments the magnitude of the anaphylactic contraction of the ileum, expressed as a percentage of contraction to a standard dose of histamine (0.1 μg/ml) was 93.6 ± 4.85% in 21 experiments. Preliminary perfusion of the intestine with potassium arsenite in a concentration of 200 μg/ml completely blocked the development of the anaphylactic reaction of the muscle in all 16 experiments in this series.

Meanwhile, just as in the experiments on human smooth muscles, the arsenic preparation in the concentrations tested did not change the excitability of the animals' smooth muscle toward histamine. For instance, the response of strips of ileum to histamine under conditions of perfusion with Krebs's solution with the addition of arsenic was 90.0 ± 1.1% ($P < 0.05$) relative to the control.

The results of these experiments showed that potassium arsenite, in the concentration tested (200 μg/ml), completely suppressed anaphylactic bronchospasm and the liberation of biologically active substances from the perfused lungs. The sensitivity of the smooth muscle of the bronchi to histamine was unchanged under these circumstances (Fig. 2).

Fowler's solution, if injected intravenously in a dose of 200 μg/kg body weight into guinea pigs immediately before the experiment (12 tests), likewise prevented the development of anaphylactic bronchospasm in vivo.

These results are evidence that inorganic arsenic blocks all the outward manifestations of the anaphylactic reaction of smooth-muscle organs: both contraction of the smooth muscle and liberation of biologically active substances. However, considering that the specific antigen may have a direct excitatory action on sensitized smooth-muscle cells [2, 3], the complete suppression of the anaphylactic reaction cannot be attributed entirely to blocking of the anaphylactic release of biologically active substances.

On the other hand, this effect likewise cannot be attributed to a disturbance of the antigen–antibody reaction, for in ring-precipitation tests and agar-precipitation tests by Ouchterlony's method [7] it was shown that arsenic did not inhibit the antigen–antibody reaction. Most probably, therefore, arsenic acts on certain other stages of the mechanism of anaphylaxis of smooth muscles, possibly by influencing fixation of antibodies to the tissues. This hypothesis is supported by the fact that preliminary treatment of the tissues for 1 h with the arsenic preparation reduced the amount of ^{131}I-labeled immunoglobulin fixed to it by 33%. The mean quantity of ^{131}I-labeled IgG fixed to the tissues of the intestine was 0.37 ± 0.01 compared with 0.56 ± 0.08 μg protein/100 g dry weight of tissue in the control.

Preliminary treatment of the smooth-muscle preparation with potassium arsenite made subsequent reproduction of the anaphylactic reaction in it impossible although, admittedly, only for 2 h. An anaphylactic reaction, to the extent of 42 ± 3.2%, could be reproduced in the segments of intestine 24 h after treatment of the preparation with arsenic. Assuming that treatment of the tissue with arsenic led to blocking of the tissue antibody receptors, no anaphylactic reaction whatsoever should have been reproducible. At the same time, we know [8] that arsenic compounds are a powerful poison for SH groups, which play an important role in the development of anaphylactic contraction of smooth muscle.

It can thus be postulated that the action of potassium arsenite is attributable both to blocking of the anaphylactic release of biologically active substances and to blocking of the enzyme systems responsible for development of the anaphylactic reaction.

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