Effect of 10 Undecen 1-YL Thiopseudourea Iodide (AHR-1911) on Rat Arterial Pressure and Capillary Permeability (37368)

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(Introduced by N. Ercoli)

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The anti-inflammatory activity of 10-Undecen-1-yl-Thiopseudourea Iodide (AHR-1911) has been shown in experimental inflammations produced by kaolin, dextran, carrageenine, and in experimental cutaneous burn (1, 3). AHR-1911 applied topically has been reported effective in inflammatory dermatological conditions (2, 11). The intradermic administration of this agent produces a reaction similar to that of histamine (3). It has been reported also that the drug causes a decrease of the arterial pressure in the anesthetized dog. (3).

The present study attempts to gain some insight about the effects of this drug on capillary permeability and its influence on vascular tone. A preliminary communication has been presented (6).

Materials and Methods. Male, Sprague–Dawley rats weighing between 250 and 300 g were anesthetized with 40 mg/kg (ip) sodium pentobarbital. The effects of AHR-1911 on the arterial pressure and its modification by different pharmacological antagonists were studied in 120 animals. For the effect of AHR-1911 on the capillary permeability 100 rats were used.

The arterial blood pressure was recorded by means of a mercury manometer connected to the femoral artery of the rat. The AHR-1911, dissolved in distilled water, was administered intravenously in a volume of 0.1 ml. Dose–response curves were obtained with the following dosages: 0.25, 0.75, 2.16 and 6.5 mg/kg AHR-1911. Moreover, groups of animals were given the following drugs at the times indicated before the administration of AHR-1911: hexamethonium bromide, 5 mg/kg, iv, 10 min; propranolol, 1 mg/kg, iv, 5 min; atropine sulphate, 0.1, 1, or 20 mg/kg, iv, 5 min; antihistamines (prometazine, diphenhydramine, or chlorpheniramine), 20 mg/kg, ip, 45 min; polymyxin B, 1.6 mg/kg, ip, daily for 3 days, injecting AHR-1911 on the fourth day. Controls received saline at the same time intervals.

For the study of the effect of AHR-1911 upon capillary permeability, a 5% solution of Evans blue in saline was administered iv, 0.05 ml/100 g body weight; 15 min later, the abdominal region of the skin was smoothly shaved and the different drugs were injected intradermally in a constant volume of 0.05 ml using a 1 ml syringe and a 27-gauge needle. The increase of the capillary permeability was quantified from the area of the blue spot appearing in the site of injection. The stained zones of the skin were dissected and removed at different time intervals and stretched out to maximum over a board, the perimeters were drawn on paper so that the areas were measured by means of a planimeter with an accuracy of $\pm$ 0.01 cm^2. The drugs were dissolved in distilled water, each animal receiving id 0.05 ml of water besides the drugs studied. The response to the drugs was evaluated by the difference in the area due to the drug and the area due to the water.

One group of rats pretreated (ip) with 20 mg/kg mepyramine, 30 min later received intradermally 50 μg AHR-1911, 500 μg histamine, 0.5 μg serotonin and distilled water. Another group, pretreated for 3 days with polymyxin B, received on the fourth day distilled water, histamine, AHR-1911 and 500 μg polymyxin B.

Statistical differences were evaluated by Student's t test; the level of significance was $p < 0.05$ (7).

Drugs used. Sodium pentobarbital (Abbott); AHR-1911 (A. H. Robins Co.); hexamethonium bromide (Parke Davis Co.); atropine sulphate (Merck); propranolol (I. C. I.); prometazine (Specia); diphenhydramine (Parke Davis); chlorpheniramine (Shering); polymyxin B sulphate (Pfizer); histamine dihydrochloride (Eastman Organic Chemicals); serotonin creatinine-sulphate (Merck); Evans blue (Merck); mepyramine (Merck A. G.). Dosages of drugs are expressed in terms of base with the exception of polymyxin B and sodium pentobarbital.

Results. The administration of AHR-1911, 0.25 mg/kg body weight produced a decrease in arterial pressure which was maximal at the dose of 6.5 mg/kg (Fig. 1). This hypotensive effect appeared almost immediately after the administration of the drug.

Pretreatment with hexamethonium, at a dose which caused a sustained hypotension, did not modify the hypotensive response produced by AHR-1911. Moreover, this response was not modified by previous administration of either propranolol or atropine although both drugs efficiently blocked the hypotensive response to isoproterenol or acetylcholine, respectively.

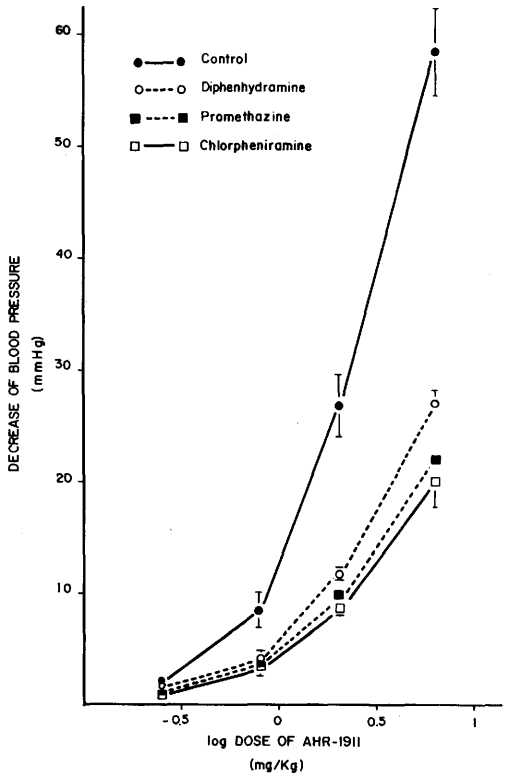

FIG. 1. Dose–response curve of the decrease in arterial pressure induced by AHR-1911 in controls and pretreated animals with diphenhydramine, promethazine or chlorpheniramine.

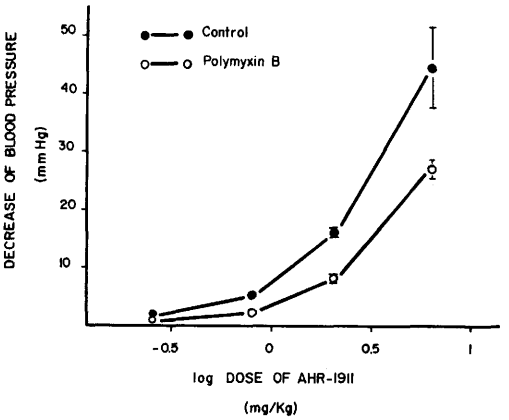

FIG. 2. Dose–response curve of the decrease in arterial pressure induced by AHR-1911 in controls and pretreated animals with polymyxin B.

The previous administration of diphenhydramine, prometazine, or chlorpheniramine produced a reduction of the hypotension induced by AHR-1911 (Fig. 1). Such a reduction was statistically significant with the doses of 0.75, 2.16, and 6.5 mg/kg for all drugs ($p < 0.01$). A similar reduction was obtained in the group of animals pretreated with polymyxin B (Fig. 2).

The intradermic administration of AHR-1911 caused an increase in the capillary permeability shown by the staining of the areas injected with the drug, where the Evans blue flowed into the extravascular space. The maximum effect was obtained 30 min after the administration of the drug. Histamine and serotonin also caused an increase in capillary permeability that reached its maximum 60 min after giving the drugs. So did polymyxin B 30 min after administration. Pretreatment with mepyramine remarkably reduced the area of staining produced by AHR-1911 or histamine at all time intervals studied; the responses to seratonin and distilled water were not modified by mepyramine

TABLE I. Effect of Mepyramine on the Increase of Capillary Permeability Induced by Various Agents.

	Controls			Mepyramine		
	Time in minutes			Time in minutes		
	15	30	60	15	30	60
	Mean ± SE[a]			Mean ± SE[a]		
AHR-1911	3.15 ± 0.6	3.94 ± 0.5	4.34 ± 0.5	1.06 ± 0.2[b]	1.07 ± 0.2[b]	1.80 ± 0.7[b]
Histamine	1.17 ± 0.2	1.84 ± 0.2	1.83 ± 0.3	0.46 ± 0.2[b]	0.46 ± 0.2[b]	0.77 ± 0.2[b]
Serotonin	1.20 ± 0.2	1.67 ± 0.2	2.20 ± 0.4	1.38 ± 0.2	1.45 ± 0.3	1.71 ± 0.3
Water	0.97 ± 0.2	1.07 ± 0.2	1.00 ± 0.1	0.72 ± 0.1	1.13 ± 0.3	1.13 ± 0.2

[a] Area in cm^2 for 8 experiments. For details, see text.
[b] Different from controls, $p < 0.01$.

(Table I). Pretreatment with polymyxin B (ip) significantly reduced the increase of capillary permeability caused by id administration of AHR-1911 or polymyxin B, not modifying the responses to id histamine or distilled water (Fig. 3).

Discussion. AHR-1911 produces in the rat a decrease of the arterial pressure related to the dosage administered. A similar effect has been shown in the dog (3), as with other thiopseudoureas (9).

Since a ganglionic blocking dose of hexamethonium did not modify the pressure response to AHR-1911, it is likely that the drug is not acting at this level. AHR-1911 does not seem to act through a cholinergic mechanism since its hypotensive response is not antagonized by atropine at dosages as high as 20 mg/kg body weight. A beta-adrenergic mechanism was ruled out by pretreatment with propranolol which did not alter the pressure response to AHR-1911. Pretreatment with various antihistamines notably reduces the hypotensive response to AHR-1911. Besides, mepyramine antagonizes the increase in capillary permeability produced by AHR-1911 to a similar degree as it antagonizes histamine, while it does not

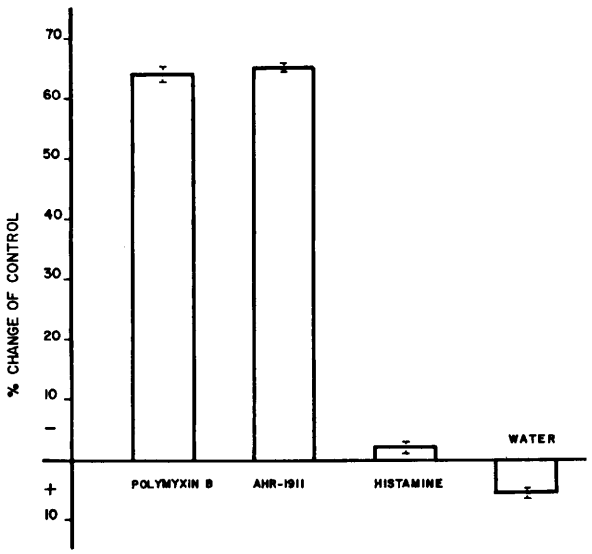

FIG. 3. Influence of polymyxin B pretreatment on the capillary permeability (staining area) induced by polymyxin B, AHR-1911, histamine or distilled water (variation compared to untreated animals).

modify the effects of serotonin and distilled water. These findings suggest that histaminergic receptors might be involved in the vascular actions of AHR-1911, which is in agreement with previous findings with other isothiouronium analogues (4, 9).

The histaminergic receptors might be acted upon either by endogenously released histamine or directly by AHR-1911. Pretreatment with polymyxin B, primarily a histamine liberator (10), decreased the hypotensive effect of AHR-1911 as well as its effects on capillary permeability. This suggests that the vascular effects of AHR-1911 are mediated by endogenously released histamine, whose decreased availability induced by pretreatment with polymyxin B (5), impairs the vascular responses of the abovementioned drug. It is worth noting that previous administration of polymyxin B antagonized, in a similar manner, the effect of AHR-1911 and polymyxin B administered id without affecting the response to histamine or distilled water. This suggests that a crossed tachyphylaxis is occurring between AHR-1911 and polymyxin B which has already been observed among histamine liberators (8).

We might conclude from our results that AHR-1911 most likely induces a liberation of endogenous histamine responsible, at least in part, for its vascular effects.

Summary. We have studied the effects of AHR-1911 on the arterial pressure and capillary permeability. The AHR-1911 caused a decrease of the arterial pressure and an increase of the capillary permeability which were antagonized by antihistamine drugs and polymyxin B. AHR-1911 probably induces a liberation of endogenous histamine responsible for these effects.

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