DIRECT ACTION OF BRADYKININ ON VASCULAR PERMEABILITY

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In experiments on rabbits and rats, bradykinin increases the permeability of the blood vessels in areas of skin not responding to histamine. Preliminary exhaustion of the tissue histamine and serotonin reserves by polymer 48/80 does not change the reactivity of the cutaneous vessels to bradykinin. This indicates a direct action of bradykinin, not mediated through histamine, on the permeability of the cutaneous vessels.

Bradykinin reproduces the cardinal signs of inflammation: disturbance of vascular permeability, changes in the blood flow, pain, emigration of leukocytes [2]. According to most published data, antihistamine agents do not inhibit the action of bradykinin on vascular permeability [7, 10]. However, these experiments do not provide conclusive proof of a direct action of bradykinin, and not one was mediated through histamine. The use of antagonists is not always effective because of the closeness of the masked cells to the vessel wall, and consequently, the rapid interaction between the liberated endogenous histamine and its substrate in the vessel wall. In addition, high specificity and activity on the antagonists are necessary in order to create a concentration in the tissues sufficiently high to inhibit the endogenous histamine. More demonstrative experiments were those of Zweifach [11], who showed that exhaustion of the histamine and serotonin reserves with the aid of compound 48/80 does not modify the response of the mesentric vessels of rats to bradykinin.

The object of the present investigation was to continue the study of this problem.

EXPERIMENTAL METHOD

Experiments were carried out on 60 Wistar rats (250-360 g), 18 guinea pigs (420-530 g), and 12 chinchilla rabbits (2.7-3.3 kg).

The tissue reserves of histamine and serotonin were exhausted by means of the substance polymer 48/80. The polymer 48/80 was injected intraperitoneally twice daily for four days in increasing concentrations: first day, each injection was 100 μg, second day, 200 μg, third day, 400 μg, and fourth day, 800 μg [9]. The effect of bradykinin on the permeability of the cutaneous vessels was studied by Ramsdell's method [8] in Oivin and Schchegel's modification [4]. The dye Evans' blue (T-1824) was injected intravenously as a 1% solution in a dose of 20 mg/kg body weight. Under these conditions application of xylene to the skin causes it to turn blue (disturbance of vascular permeability) after 4-7 min, in agreement with data in the literature [4]. Various doses of bradykinin in 0.1 ml physiological saline were injected intradermally 5 min after injection of the dye. Physiological saline was injected into control areas of skin. The criterion of a disturbance of vascular permeability was the appearance of a blue papule, not less than 7 mm in diameter, in the course of 10 min.

Diphenhydramine hydrochloride and dimeboline hydrochloride were injected intramuscularly 30 min before injection of the dye in a dose of 10 mg/kg.

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To study the action of bradykinin on vessels not responding to histamine, areas of skin infiltrated with histamine (5 μg, 3 times at intervals of 15 min) were used. A solution of the dye was injected after 40 min. Histamine (5 μg) was injected into the control areas of skin, and bradykinin (0.5 μg) into the experimental areas and the appearance and intensity of coloration of the papules were recorded. The numerical data were analyzed by Student's method and by Roth's modification of the Litchfield–Wilcoxon probit analysis method [1].

Diphenhydramine hydrochloride (dimedrol, Riga Pharmaceutical Chemical Factory), dimeboline hydrochloride and polymer 48/80 (Burroughs, Wellcome, and Co., USA), and synthetic bradykinin (Sandoz, Switzerland)*, were used in the investigation.

EXPERIMENTAL RESULTS

The criterion for comparing the mediators of permeability was the dose of bradykinin disturbing the permeability of the cutaneous vessels in 50% of animals (ED_{50}), and in healthy rabbits, guinea pigs, and rats this was 0.0007, 0.001, and 63 ng, respectively. Preliminary injection of antihistamine compounds diphenhydramine and dimeboline inhibited the action of bradykinin on the permeability of the cutaneous vessels. Diphenhydramine inhibited the action of bradykinin least effectively. ED_{50} for rabbits and guinea pigs receiving a preliminary dose of diphenhydramine was 0.7 and 5.6 ng, respectively. Dimeboline inhibited the action of bradykinin in rabbits (ED_{50} = 0.5 ng), but had no appreciable effect in the experiments on guinea pigs (ED_{50} = 0.006 ng). Preliminary administration of polymer 48/80 to the rats caused virtually no change in the reactivity of the cutaneous vessels to bradykinin. The value of ED_{50} for bradykinin in treated animals was 65 ng, not significantly different from ED_{50} obtained in experiments on the untreated rats.

The cutaneous vessels are known to become adapted to histamine as a permeability factor, after a certain time interval [5, 6]. In the present experiments, adaptation of the cutaneous vessels to histamine developed in rabbits and rats after exposure to histamine in 30 min. Unlike histamine, bradykinin increased the permeability of the cutaneous vessels in rabbits even after acting for 1 h. Intradermal injection of bradykinin into areas of skin not responding to histamine showed that the sensitivity of the vessels in these areas of the skin to the action of bradykinin was preserved. The intensity of coloring (on a 5-point system) of the papules with physiological saline and of the areas of skin not responding to histamine (infiltrated with histamine) after injection of 0.5 μg bradykinin was 4.9±0.12 and 4.9±0.2, respectively, i.e., virtually the same.

A substance which is considered to play the role of mediator of inflammation must satisfy a number of demands: 1) it must be able to evoke at least some, if not all, of the cardinal signs of inflammation (increased vascular permeability, emigration of leukocytes, pain, and so on); 2) it must be found in inflamed tissues in concentrations which are effective in biological tests; 3) it must act immediately and not indirectly through activation of endogenous factors on inflammation. The use of powerful and specific antagonists and exhaustion of the tissue histamine or serotonin reserves by injection of the corresponding liberators may prove extremely useful in these cases. The present investigation showed that both diphenhydramine and dimeboline inhibited the action of bradykinin on cutaneous vascular permeability. Diphenhydramine inhibited the action of bradykinin on permeability of the cutaneous vessels in rabbits 1.5 times more actively than dimeboline, and 18 times more actively than in the case of the cutaneous vessels of guinea pigs. It has previously been shown that dimeboline is 95 times stronger than diphenhydramine as an antihistamine agent [3]. This indicates a nonspecific inhibition of the action of bradykinin by these compounds, and suggests that bradykinin acts directly on the permeability of the cutaneous vessels. This conclusion is also confirmed by experiments carried out with polymer 48/80, a liberator of histamine and serotonin. The results of these experiments showed that injection of polymer 48/80 did not alter the reactivity of the cutaneous vessels to bradykinin, indicating that the action of bradykinin on permeability is direct and not mediated through histamine or serotonin. This is also confirmed by experiments which showed that tachyphylaxis of the cutaneous vessels does not develop to bradykinin, as it does to histamine. The ability of the bradykinin to increase vascular permeability in areas of skin not responding to histamine suggests the existence of different substrates and, consequently, of different intimate mechanisms of the auction of bradykinin and histamine on the permeability of the cutaneous vessels.

* The dimeboline hydrochloride was generously provided by Professor K. S. Shadurskii and the bradykinin by Drs. K. Neff and B. Larsonneur (Sandoz A. G.).

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