ENERGETIC ASPECTS OF THE ACTION OF HISTAMINE AND BRADYKININ ON VASCULAR PERMEABILITY

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Experiments on rabbits and rats showed that ATP restores the vascular response of the skin to bradykinin and histamine to normal when inhibited by sodium cyanide. The results of the investigations confirmed the hypothesis of the active character, coupled with energy expenditure, of the increased permeability of the vessels by permeability factors and they demonstrated the important role of high-energy phosphorus compounds in this mechanism.

KEY WORDS: histamine; bradykinin; vascular permeability; adenosine triphosphate.

During the action of inflammatory stimuli on the tissues permeability factors (histamine, kinins, serotonin) are liberated or formed; they cause rounding of the endothelial cells and they increase the permeability of the endothelial membrane. Rounding of the endothelial cells is linked with a change in the state of their contractile structures [8]. On this basis it was postulated that the contraction of these structures is coupled with expenditure of energy produced by aerobic respiration. Experiments have shown that the action of permeability factors is blocked by the use of cyanides in doses inhibiting tissue respiration [6]. In hypoxia induced by cyanide, the resynthesis of high-energy compounds, especially ATP, in the endothelial cells may be sharply reduced.

This investigation was carried out to test the above hypothesis.

TABLE 1. Effect of ATP on Response of Skin Vessels of a Rabbit to Permeability Factors, when Inhibited by NaCN (10^{-2} M)

Permeability mediator	Physiological saline (control 1)	Physiological saline + NaCN (control 2)	ATP (10^{-2}M) + NaCN
Histamine (10 μg)	30/30	4/30	30/30*
Bradykinin (0.5 μg)	30/30	5/30	30/30*

Legend. Here and in Tables 2 and 3 numerator represents number of animals with disturbed vascular permeability, denominator total number of animals. Results differing significantly ($P < 0.05$) from control 2 are marked by an asterisk.

EXPERIMENTAL METHOD

Experiments were carried out on 30 Wistar rats (180-230 g) and 25 chinchilla rabbits (2.7-3.3 kg). The effect of mediators on vascular permeability was studied by a modified [4] Ramsdell's method [9]. A 1% solution of the dye Evans' Blue (T-1824) was injected intravenously in a dose of 20 mg/kg. After a delay of 5 min, 0.1 ml ATP solution (10^{-2}-10^{-3} M) was injected into the previously shaved skin of the flank of the rabbits and rats. Two minutes after the injection of ATP, 0.1 ml NaCN solution (10^{-2} M) was injected intradermally into the same papules. Bradykinin (0.5-1.0 μg) or histamine (10 μg) was injected 10 min later into the same areas of the skin.

The results were analyzed by Fisher's method for a fourfold table [2].

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TABLE 2. Effect of ATP on Response of Skin Vessels of Rats to Permeability Factors when Inhibited by NaCN (10^{-2}M)

Permeability mediator	Physiological saline (control 1)	Physiological saline + NaCN (control 2)	ATP (10^{-3}M) + NaCN
Histamine (10 μg)	21/21	4/21	14/21*
Bradykinin (1 μg)	17/17	0/17	10/17*

TABLE 3. Effect of ATP and AMP on Response of Skin Vessels of a Rabbit to Histamine (10 g) when Inhibited by NaCN (10^{-2} M)

Concentration of ATP and AMP	Physiological saline (control 1)	Physiological saline + NaCN (control 2)	AMP + NaCN	ATP + NaCN
10^{-3} M	20/20	6/20	10/20	15/20*
$5 \cdot 10^{-3}$ M	12/12	3/12	6/12*	12/12*

Synthetic bradykinin (Sandoz, Switzerland), histamine hydrochloride (Riga Pharmaceutical Chemical Factory), Evans' Blue dye (Reanal, Hungary), and NaCN (Chemapol, Czechoslovakia) were used.

EXPERIMENTAL RESULTS

In the experiments on rabbits (Table 1) histamine (10 μg) and bradykinin (0.5 μg) were injected into intact areas of skin, inducing a disturbance of vascular permeability in every case. Permeability mediators, injected into areas of skin infiltrated with cyanide, caused virtually no disturbance of vascular permeability ($P < 0.001$). The preliminary injection of ATP (10^{-2} M) into areas of skin into which NaCN solution was later injected in every case restored the ability of the vessels to react to the permeability mediators.

In the experiments on rats (Table 2) ATP in a concentration of 10^{-2} M in some cases itself induced a disturbance of vascular permeability, so that in the main series of experiments a concentration of 10^{-3} M was used: this gave no such effect although, despite the decrease in the ATP concentration, it significantly weakened the inhibitory effect of cyanide on the action of the permeability factors.

In a separate series of experiments on rabbits (Table 3) two derivatives of adenylic acid – ATP and AMP – were compared. As Table 3 shows, the preliminary injection of AMP (10^{-3}M) did not significantly change the inhibited response of the rabbit's skin vessels to histamine. Preliminary injection of ATP in the same concentration increased by 2.5 times the ability of the skin vessels, when infiltrated with cyanide, to react to injection of histamine by increased permeability. An increase in the AMP concentration to $5 \cdot 10^{-3}$ M on the average increased the reactivity of the skin vessels to histamine ($P < 0.05$). However, in 50% of cases no disturbance of vascular permeability developed under these circumstances. The injection of ATP in the same concentration in all cases restored the ability of the skin vessels to react by increased permeability to the injection of histamine.

It is stated in the literature that ATP is a mediator of inflammation [1], although serious objections have been raised. Some workers [3, 5, 7] have shown that ATP in doses of up to 1000 μg ($\approx 2 \cdot 10^{-2}$ M) does not increase the vascular permeability in healthy rabbits. The present experiments confirmed this statement.

The results of the present investigations support the view of the active character of the increased permeability of the vessels under the influence of true permeability factors and its link with energy expenditure; they indicate the importance of high-energy phosphorus compounds in this mechanism.

In the light of these facts it can be postulated that the main cause of the decrease in inflammatory reactivity taking place under apparently the most widely different pathological conditions, is evidently weakening of the synthesis of high-energy compounds or the inhibition of enzyme systems as a result of which there is a deficit in the production of energy required both to liberate or to form the permeability factors and for the contractile reaction of the endothelial cells.

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