CYPROHEPTADINE AS AN INHIBITOR OF BRADYKININ EFFECTS

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The effect of cyproheptadine, an inhibitory of serotonin and histamine, on the effects of exogenous and endogenous bradykinin was investigated. Cyproheptadine inhibited the effect of bradykinin on a segment of guinea pig intestine in vitro, abolished the hypotensive action of bradykinin on rats in vivo, and blocked constriction of the blood vessels of the rabbit ear and the fall in the blood kininogen level caused by injection of pyrogenal.

KEY WORDS: bradykinin; action block; cyproheptadine.

Considering the many facts indicating a role of kinins in various pathological responses, it is important to search for preparations that block the action of bradykinin. Comparison of the chemical structure of bradykinin inhibitors would also help to elucidate the structure of its receptor.

In the investigation described below the effect of cyproheptadine, an inhibitor of serotonin and histamine [1, 8], on the effect of exogenous and endogenous bradykinin was studied.

EXPERIMENTAL METHOD

Three series of experiments were carried out. Responses to bradykinin and other preparations before and after addition of the inhibitor were studied on the isolated segment of guinea pig intestine. The section of intestine was placed in a 20-ml bath containing Tyrode's nutrient solution.

Hypotensive responses to bradykinin and other preparations injected intravenously before and after the cycloheptadine were studied in rats anesthetized with urethane. The mean blood pressure was recorded in the carotid artery with a mercury manometer. All the substances, made up in physiological saline, were injected into the femoral vein in a dose of 0.1-0.3 ml.

In experiments on unanesthetized rabbits the action of cyproheptadine was studied on the effects of endogenous bradykinin. The substance pyrogenal, obtained at the N. F. Gamaleya Institute of Epidemiology and Microbiology [2], was used as the kinin-releasing factor. Changes in the temperature of the rabbit's ear, reflecting the magnitude of the peripheral circulation, were recorded every 5 min by means of a thermistor.

The experiments were carried out in an ambient temperature of 20-22° C. At various time intervals before and after injection of the preparations the level of the bradykinin precursor, kininogen, in the rabbit's blood plasma was determined [4].

The following preparations were used: bradykinin triacetate (Sandoz, Switzerland); serotonin–creatine–sulfate (Reanal, Hungary); trasylol (Bayer, West Germany); histamine, acetylcholine, and other preparations of Soviet manufacture; cyproheptadine – 4-(5-dibenzo[a.e]cycloheptatrienyliden)-1-methylpiperidine hydrochloride (Merck, West Germany).

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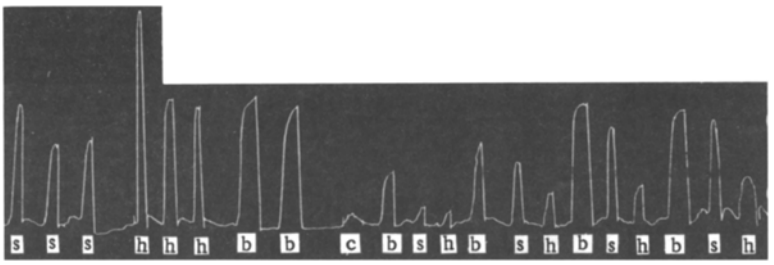

Fig. 1. Duration of inhibitory action of cyproheptadine on effect of bradykinin, serotonin, and histamine on segment of guinea pig intestine. Final concentrations of substance in bath (in g/ml): serotonin (s) $0.5 \cdot 10^{-8}$; histamine (h) $0.5 \cdot 10^{-8}$; bradykinin (b) $1.2 \cdot 10^{-9}$; cyproheptadine (c) $1.25 \cdot 10^{-8}$. Intervals between tests 4 min. Cyproheptadine removed from bath after 1 min.

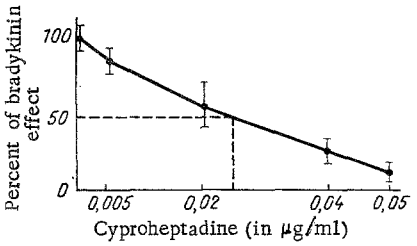

Fig. 2. Inhibition of bradykinin effect on segment of guinea pig intestine depending on cyproheptadine concentration. Concentration of bradykinin $1.2 \cdot 10^{-9}$ g/ml. Mean results of 5 experiments.

EXPERIMENTAL RESULTS AND DISCUSSION

In the experiments of series I the blocking action of cyproheptadine on contractions of the isolated segment of guinea pig intestine induced by bradykinin was investigated. This effect was compared with the analogous action of the inhibitor on histamine and serotonin. As Fig. 1 shows, cyproheptadine in a final concentration of 1.25 and 10^{-8} g/ml blocked the effect of bradykinin to a rather lesser degree than that of serotonin and histamine. This inhibitory action of the inhibitor was reversible; the effect of bradykinin and serotonin were restored almost simultaneously after rinsing the intestine to remove cyproheptadine, but the effect of histamine was restored later.

The dependence of the bradykinin-inhibitory action of cyproheptadine on its dose is shown in Fig. 2. According to calculation, $8 \cdot 10^{-8}$ M cyproheptadine is the dose that inhibits by 50% the effect of $2.5 \cdot 10^{-9}$ M bradykinin.

In the experiments of series II on rats the inhibitory action of cyproheptadine (0.9 mg/kg) on the hypotensive effect of 0.6 μg/g bradykinin, injected intravenously, was studied. This dose of the inhibitor completely abolished the effect of bradykinin and also of histamine (1 μg/kg); the hypotensive responses to acetylcholine (1 μg/kg) under these circumstances was only very slightly altered.

The results show that cyproheptadine depresses the effect of bradykinin in experiments both in vitro and in vivo.

In the next experiment the effect of cyproheptadine on the effect of endogenous bradykinin was studied. The substance pyrogenal, used for the production of experimental fever, was used as the factor activating the kallikrein–kinin system. The experiments were performed in this way because it has been shown that following administration of pyrogenal the blood kininogen level in man is reduced by 30%. This effect is due to the liberation of lysosomal enzymes followed by kallikrein activation [3].

Intravenous injection of pyrogenal (1 μg/kg) into a rabbit led to rapid rise of rectal temperature, preceded by a sharp decrease in the temperature of the ear and in the plasma kininogen level (Fig. 3, I, III).

The fall of temperature of the rabbit's ear after administration of pyrogenal is connected with slowing of the peripheral circulation [5]. Guth et al. obtained evidence of the constrictor action of bradykinin on the blood vessels of the rabbit's ear which accompanies the systemic hypotensive action of the polypeptide [6]. In the present case also, the fall of temperature of the rabbit's ear after administration of pyrogenal was evidently due to the liberation of bradykinin, as shown by a decrease in the kininogen concentration in the blood. Vasoconstriction in the rabbit ear associated with administration of pyrogenal also was abolished by preliminary administration of trasylol (4000 units/kg, 3 injections), an inhibitor of kallikrein and other proteinases, to the animal. This indicates that the temperature (vasoconstrictor) response to pyrogenal is based on activation of the endogenous kallikrein–kininogen–bradykinin system.

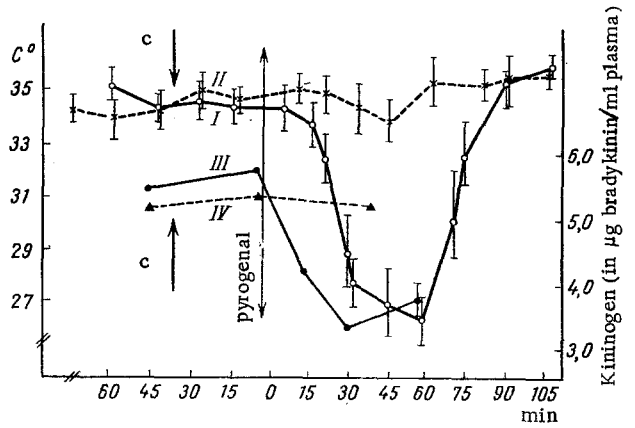

Fig. 3. Temperature of rabbit's ear and plasma kininogen level after injection of pyrogenal (1 μg/kg) and cyproheptadine (c) (0.2 mg/kg): I) ear temperature after injection of pyrogenal (in °C); II) ear temperature after injection of cyproheptadine and pyrogenal; III) blood kininogen level after injection of pyrogenal; IV) kininogen level after injection of cyproheptadine and pyrogenal. Mean results for 16 experiments based on changing temperature and of 6 experiments based on kininogen determination.

Preliminary injection of cyproheptadine into the animal abolished the fall of temperature in the rabbit's ear caused by pyrogenal. The kininogen level also was unchanged under these circumstances (Fig. 3 II, IV). Consequently, pyrogenal activation of the kinin system was blocked by cyproheptadine, on account of which no liberation of bradykinin took place and its constrictor effect on the vessels of the rabbit's ear was prevented.

Inhibition of the action of bradykinin by cyproheptadine has been mentioned earlier [7]. The results described in this paper demonstrate the inhibitory action of cyproheptadine on the effect of exogenous and endogenous bradykinin. Since bradykinin is a product of the multistage kallikrein–kinin system, it is important to note that the effect of cyproheptadine is brought about both at the level of kallikrein activation and at the last stage – the level of bradykinin itself.

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