An antihistamine compound with potent antibradykinin activity

Bradykinin is considered to play an important role in numerous pathological processes, and an effective antagonist *in vivo* may be of value in controlling pathological reactions induced by endogenous bradykinin. Certain antihistamine compounds, particularly phenothiazine derivatives, possess antibradykinin activity *in vitro* when tested on the isolated ileum of the guinea-pig (Mariani, 1961; Rocha e Silva & Leme, 1963; Horowitz & Mashford, 1969). Some thioxanthene and dibenzocycloheptene derivatives also exert powerful antibradykinin activity *in vitro* (Leme & Rocha e Silva, 1965). Nevertheless, inhibition *in vivo* has been difficult to demonstrate and, even then, antagonists such as the salicylates and the fenamates are often effective only in one or two preparations, as, for example, against the bronchospasm induced by bradykinin in guinea-pigs (Collier & Shorley, 1963).

The present report relates to the effectiveness of a potent antihistamine compound (halopyramine) both in reducing the action of bradykinin on the rat isolated uterus and on capillaries in rat skin, and in reducing thermic oedema in rat paws which results from the formation and release of endogenous bradykinin (Starr & West, 1967). Halopyramine hydrochloride (Synopen, Geigy), a chlorobenzyldimethylpyridyl derivative of ethylenediamine, is a white powder, readily soluble in water, and in all of the following experiments a stock solution was made by dissolving it in normal saline to provide a 0·1% (w/v) solution.

On the isolated uterus of a rat in oestrus, halopyramine was found to be an effective antagonist of bradykinin, a concentration of 1×10^{-7} in six experiments reducing the contractions produced with 1 ng bradykinin (in a 5 ml bath) by about 35% and with 0·5 ng by about 49%. The antagonist was quickly removed from the preparation by washing (Fig. 1a). Concentrations of 2×10^{-7} g did not alter the 5-hydroxytryptamine responses and histamine is inactive. Doses of bradykinin (1·25 and 2·5 μg) were next injected intradermally into depilated skin of rats with azovan blue dye (10 mg/kg) in their circulation. Groups of 15 adult albino animals were used, some of which had been injected 5 min before the bradykinin with halopyramine intraperitoneally (10 mg/kg). Twenty min after the bradykinin injection, the rats were killed and their dorsal skin was removed, cleaned of fat and dried at 56°. The blue dye exuded into the injection sites was extracted by the method of Judah & Willoughby (1962) and assayed using a Beckman spectrophotometer. Halopyramine significantly reduced the amount of dye released from the capillaries by the bradykinin (see Fig. 1b). Intraperitoneal doses of 10 mg/kg did not alter the blueing of rat skin induced by 5-hydroxytryptamine or histamine.

In other experiments, the hindpaws of groups of 15 adult albino rats under light ether anaesthesia were heated at 46·5° for 30 min (Rocha e Silva & Antonio, 1960), some of the groups being injected 5 min before the heating with either 5 or 10 mg/kg halopyramine intraperitoneally. Thirty min later, the rats were killed and the size of the oedema was expressed as a percentage increase in limb weight compared with the weight of the opposite unheated limb. This method of assessing oedema gave results which were comparable with those obtained using plethysmography. The higher dose of halopyramine significantly reduced the swelling resulting from the heat application (Fig. 1c). Starr & West (1967) have previously reported that large doses of more specific antihistamine compounds (as, for example, mepyramine, 50 mg/kg) had no effect on the thermic oedema and did not reduce the local capillary effect of bradykinin although several non-steroidal anti-inflammatory compounds were potent inhibitors.

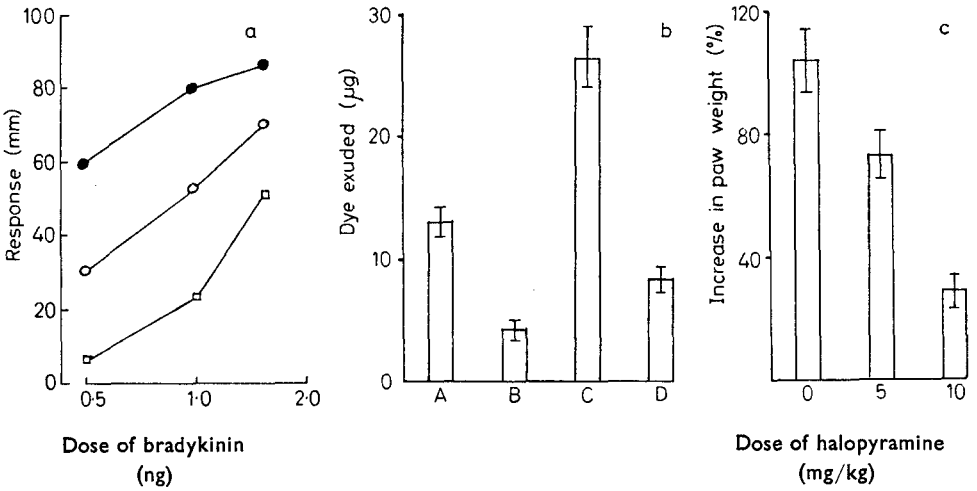

FIG. 1a. Dose-response curves of rat uterus to bradykinin. Effect of halopyramine. Mean of 6 experiments. ●—● control. ○—○ 0·1 μg/ml of drug. □—□ 0·2 μg/ml of drug.

b. Effect of intraperitoneal doses of 10 mg/kg halopyramine (B and D) on the dye exudate (μg) in rat skin produced by the intradermal injection of bradykinin (A and B, 1·25 μg: C and D, 2·5 μg). Results are the means (± s.e.) of 15 experiments.

c. Effect of intraperitoneal doses of halopyramine (mg/kg) on the % increase in paw weight of rats after heating at 46·5° for 30 min. Results are the means (± s.e.) of 15 experiments.

The present study shows that halopyramine possesses antibradykinin activity both *in vitro* and *in vivo*, and significantly reduces the thermic oedema resulting from the release of endogenous bradykinin. This compound may well lessen inflammation in clinical conditions.

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