ON THE HISTAMINE RECEPTOR OF THE CANINE MYOCARDIUM AND CORONARY VASCULATURE*

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Abstract - To identify the histamine-receptors in the canine myocardium, experiments were performed in the canine heart-lung preparation supported by a donor. Smaller doses of histamine produced only an increase in the coronary blood flow. Positive inotropic and chronotropic effects appeared with larger doses. The increase in the coronary blood flow was associated with only a minimal increase in the myocardial oxygen consumption. Pretreatment of the preparation with a prototype H1-receptor antagonist, mepyramine, resulted in an abolishment of the positive chronotropic effect and a partial inhibition of the coronary vasodilatory effect, indicating that the histamine-receptors in the dog atrium subserving the chronotropic effect are to be classified as H1-type. After a representative H2-receptor antagonist, metiamide, the positive chronotropic effect remained unaffected, while there was a partial inhibition of the coronary vasodilatory effect. A combined use of both the H1- and H2-receptor antagonists brought about a complete suppression of the positive inotropic and the coronary vasodilatory effects of histamine. These findings indicate that the histamine-receptors in the coronary vasculature belong to the same type of receptors as those in the peripheral blood vessels, and that those in the canine ventricular myocardium cannot be classified either as H1 or H2.

Gastric secretory and cardiac stimulatory effects of histamine which could not be blocked by classical antihistaminics have recently been reported to be blocked by a new type of compounds such as burimamide and metiamide and the receptor subserving these two effects of histamine have been classified as H2-type receptors (1-5), in contrast to the classical histamine receptor, which is now designated as H1-type receptor. Although the later works performed with the atrial preparation of the guinea pig (6-7) suggested that the positive inotropic effect of histamine is mediated through H1-receptors, since the positive inotropic effects in the left atria are blocked by H1-blocking agents, Reinhardt et al. (8) reached the conclusion that only H2-receptors exist in the ventricular myocardium, substantiating the initial findings of several investigators. Using the right ventricular strips of the guinea pig, Verma and McNeill (9) also suggested that the major histamine receptor in the ventricular myocardium of the guinea pig is of H2-type. H1-receptors are either few in number or do not have a high affinity for agonists. However, very recently, Chiba (10)

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reported that the positive inotropic and chronotropic effects of histamine in the isolated dog atrium perfused with arterial blood led from a carotid artery of the support dog were not blocked by selective \( H_1 \)-receptor blocking agents, burimamide or metiamide, but significantly suppressed by an adequate dose of \( H_2 \)-receptor antagonist, tripelenamine or diphenhydramine.

In view of this discrepancy, the present study was undertaken to characterize the histamine receptor of the canine myocardium, using the heart-lung preparations of the dog supported by a donor. Attention was also directed towards the histamine receptor subserving the coronary vasodilatory effect of this compound.

**MATERIALS AND METHODS**

Experiments were performed in the canine heart-lung preparation supported by a donor, the details of which were described in previous publications (11, 12). Mongrel dogs of either sex weighing between 6 and 12 kg were anesthetized with an intraperitoneal administration of 35 mg/kg of sodium pentobarbital and the heart-lung preparations were prepared according to the Krayer-Mendez modifications of the original Starling method. Donor dogs weighing 22-36 kg were anesthetized with an intravenous administration of \( \alpha \)-chloralose (45 mg/kg) and urethane (450 mg/kg) after premedication with morphine hydrochloride (1.5 mg/kg) administered subcutaneously.

Drugs used were histamine dihydrochloride (Sigma Chemical), dl-noradrenaline (Sankyo), mepyramine bitartrate (K & K), metiamide (Smith, Kline & French), propranolol (ICI Japan) and Kö 1400 (Hokuriku Seiyaku). Drugs were injected over a 10 sec period into the rubber tubing leading to the venous cannula of the preparation. Blockers were injected into the venous reservoir.

**RESULTS**

**Effects of histamine**

Fig. 1 illustrates a representative record of the effects of histamine on the canine heart-lung preparation supported by a donor. Starting with 10 \( \mu \)g, histamine produced a dose-related increase in the coronary blood flow. Positive inotropic and chronotropic effects appeared at higher doses. However, even with high doses the cardiac effects were not so marked as the increase in the coronary blood flow. For comparison, the effects of 3 \( \mu \)g of noradrenaline on this preparation are depicted together with those of 200 \( \mu \)g of histamine in Fig. 2. In Table 1 are summarized the numerical data of the effects of histamine on the cardiohemodynamic parameters.

In Fig. 3 is plotted the increase in the coronary blood flow produced by 50-300 \( \mu \)g of histamine against the increase in the myocardial oxygen consumption. Only a slight increase in the oxygen consumption was observed, indicating that the substance exerted a direct dilatoratory effect on the coronary vasculature.

**Effects of antihistamines**

Pretreatment of the preparation with a representative histamine \( H_2 \)-receptor antagonist,
metiamide, in a dose of 10–20 mg, produced a definite suppression of the increase in the coronary flow, while the positive inotropic and chronotropic effects remained practically unchanged.

**Fig. 1.** Effects of histamine on the canine heart-lung preparation supported by a donor (Exp. No. 152; dog, male, 10 kg; heart weight 84 g). Total blood volume at the beginning of the experiment was 1200 ml. SOP: systemic cardiac output. CF: coronary blood flow. RAP: right atrial pressure. HR: heart rate per minute.

**Fig. 2.** Effects of histamine on the canine heart-lung preparation supported by a donor as compared with those of noradrenaline. (Exp. No. 155; dog, male 9 kg; heart weight 72 g). Total blood volume at the beginning of the experiment was 1000 ml.

**Fig. 3.** Effects of histamine (50–300 μg) on the relation between the changes in the coronary flow and the changes in the myocardial oxygen consumption. ΔCor. flow (%): changes in the coronary flow expressed as percent of the initial value. ΔO₂ consumption (%): changes in the myocardial oxygen consumption expressed as percent of the initial value.
unaffected, as illustrated in Fig. 4 and Table 1. The positive chronotropic effect was at times even potentiated and irregularities of sinus origin were observed as shown in Fig. 4. Metiamide itself produced no significant effects either on the cardiac function or on the coronary vasculature at dosages, at which it produced a definite inhibition of the increase in the coronary flow.

A prototype H₁-receptor antagonist, mepyramine, in doses of 2–5 mg, resulted in a complete inhibition of the positive chronotropic effects and a definite inhibition of the increase in the coronary blood flow (Fig. 5 and Table 1). The positive inotropic effect of histamine remained unchanged even in the presence of this dose of mepyramine.

Mepyramine itself produced a slight negative chronotropic effect in doses above 2 mg: Before mepyramine, the heart rate was 138.8 ± 7.3, while it was 130.0 ± 9.3 after 2.5 mg of mepyramine (n=7, P<0.05).

Combined use of both the H₁- and H₂-receptor antagonists, in doses which did not
produce definite inhibitory effects, if given separately, brought about a complete blockade of all the cardio-stimulatory as well as the coronary vasodilatatory effects of histamine, as shown in Figs. 4 and 5 and in Table 1. Antagonistic effects of either mepyramine (3 mg or more) or metiamide (10 mg or more) last for more than two hours in this preparation.

Effects of adrenergic β-blocking agents

Pretreatment of the preparation with adrenergic beta-blocking agents, propranolol (0.1–0.3 mg) or Kø 1400 (1 mg), which was capable of abolishing the effects of 3–10 µg of noradrenaline, was without any significant effect either on the cardio-stimulatory effects or on the coronary vasodilatatory effect of histamine.

DISCUSSIONS

The present study clearly demonstrated that a combined used of both the H1- and H2-receptor antagonists is needed to suppress the positive inotropic effect of histamine in the canine myocardium. Either H1- or H2-antagonists was without effects, if administered separately. As far as we know, this is the first demonstration of the histamine receptors that cannot be classified either as H1 or H2. In contrast, the positive chronotrophic effect was abolished with H1-receptor antagonist, and such is in agreement with the recent findings of Chiba (10). Thus, unlike the histamine-receptor in the guinea pig atrium, the histamine receptor in the dog atrial myocardium subserving the positive chronotropic effect is to be classified as H2-type receptor.

Flacke et al. (13) demonstrated in the dog heart-lung preparation that the increase in the heart rate produced by larger doses of histamine was blocked by propranolol, and suggested that the substance had a catecholamine-releasing action. The catecholamine-
releasing action of histamine was also demonstrated in the isolated atrial preparation of the guinea pig concerning the mechanism of action of hydralazine and the receptor responsible for this action of histamine was classified as H₁ (14). However, in the present study the positive chronotropic effects of this compound, although inhibited with H₁-receptor blocking agent, were not affected with adrenergic beta-blocking agents, invalidating the hypothesis that the positive chronotropic effect of histamine is related to a release of catecholamine.

In the present study, only an increase in the coronary blood flow was observed with smaller doses of histamine in the complete absence of the cardio-stimulatory effects, indicating that a predominant effect of this substance in the canine myocardium is not a cardio-stimulation, but a direct dilatation of the coronary vasculature.

Although the increase in the coronary blood flow became much attenuated after pretreatment of the preparation with the H₁-antagonist, mepyramine, or the H₂-antagonist, metiamide a combined use of both the H₁- and H₂-antagonists was needed to obtain complete abolishment of the coronary vasodilatory effect of histamine. It is, therefore, concluded that the histamine receptors in the canine coronary vasculature belong to the same type of receptors as those in the peripheral blood vessels. This conclusion is in agreement with the recent report by Giles et al. (15). Histamine receptors subserving the coronary vasodilatation were classified either as H₁ (3 and 16) or H₂ (6 and 17). However, the conclusions were based on the studies, which could not differentiate between the direct vasodilatory effect and the vasodilatation attributable to a cardio-stimulation. Only one report is, therefore, worth mentioning: Broadley (16) separated the histamine-induced coronary vascular response of the guinea pig into three phases. The first stage of the response manifested as a fall in perfusion pressure was considered to be direct vasodilatory effect, since it appeared before the onset of any myocardial changes. As this stage of the response was antagonized by mepyramine, he classified the histamine-receptor subserving the coronary vasodilatation as H₁-type. The discrepancy between the results of Broadley (16) and our own can be ascribed to the species difference as described with respect to the cardio-stimulatory actions of this compound in the "introduction" section.

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