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Dissociation of cimetidine effects on inotropic and chronotropic action in cardiac anaphylaxis[1]

GUO Zhao-Gui, QIU Rong

(Research Section of Pharmacology, Hu-nan Medical University, Changsha 410078)

Abstract The changes of heart rate (HR) and dP/dt_{max} elicited by challenging the sensitized heart and by a bolus injection of histamine in the presence of cimetidine were observed. The results showed that cimetidine did not completely inhibit the positive chronotropic effect in cardiac anaphylaxis. The increase in HR elicited by exogenous histamine on sensitized heart was completely abolished. Cimetidine inhibited the positive inotropic and chronotropic effect of histamine on normal heart in a dose-dependent manner. It is suggested either an H_2 receptor subtype or concomitant with the release of histamine, other mediators eliciting positive chronotropism in cardiac anaphylaxis may exist.

Key words cardiac anaphylaxis; isolated working heart; histamine; cimetidine; myocardial contraction; heart rate

Obvious positive inotropic and chronotropic effects have been observed when histamine H_2 receptors are stimulated. Levi *et al* reported that the short increases in both cardiac contraction and heart rate (HR) in cardiac anaphylaxis were mediated by histamine H_2 receptors[1]. When studying cardiac anaphylaxis in the presence of the H_1 antagonist pyrilamine and the H_2 antagonist cimetidine (both at 3 μmol/L) or cimetidine alone (3 μmol/L) in isolated working guinea pig hearts, we found that as the augmentation of cardiac function parameters in phase I was inhibited, the increase in HR was not significantly affected[2]. In order to investigate the mechanism of the dissociation of the inhibitory effect of cimetidine on the positive inotropic and chronotropic action, we observed the changes in HR and dP/dt_{max} which occurred in phase I of cardiac anaphylaxis in the presence of different concentrations of cimetidine, and compared them with the effects of exogenous histamine. The dose-response relationship between HR and dP/dt_{max} for histamine at various concentrations of cimetidine was also studied.

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Methods

Cardiac anaphylaxis in the presence of cimetidine The method of sensitization and the experimental model were the same as described before[3]. Isolated working guinea pig hearts were perfused for 20 min before experiment, by then HR and other cardiac function parameters had reached a steady state. Hearts were continuously perfused with cimetidine at concentrations of 3, 10 and 100 μmol/L, respectively, for 10 min before antigen challenge. 5 mg ovalbumin in 0.2 ml of warm oxygenated K-H solution were injected rapidly into the heart via an atrial cannula for challenge. The changes in HR and dP/dt_{max} were measured.

Effects of exogenous histamine on sensitized working guinea pig hearts in the presence of cimetidine Sensitized working hearts were perfused with cimetidine at concentrations of 3, 10 and 100 μmol/L, respectively, for 10 min. Histamine 5 μg was injected into heart via an atrial cannula,

Histamine dose-response relationship in normal working guinea pig hearts in the presence of cimetidine Histamine 0.1, 0.3, 1, 3, 10 and 30 μmol/L was added into the perfusion solution in a cumulative manner in order to test the dose-response relationship after 10 min perfusion of cimetidine at doses of 3 and 10 μmol/L, respectively. The effects of each dose of histamine were observed for 5 min. Changes in HR and dP/dt_{max} were measured and expressed as the percentage variation from the control values.

Drugs Crystallized ovalbumin was obtained from the Shanghai Institute of Biochemistry. Cimetidine and histamine were purchased from Sigma Company.

Results

Effects of cimetidine on HR and dP/dt_{max} in augmentation phase of cardiac anaphylaxis When the sensitized heart was challenged, HR and dP/dt_{max} increased by 30.8 and 38.4%, respectively, ($P<0.01$) at about 1 min after challenge in the augmentation phase. The peak increase in dP/dt_{max} occurred 30±20 s earlier than that of HR. Cimetidine at 3 μmol/L did not significantly inhibit the enhancement of HR (from 30.8 to 26.8%, $P>0.05$). At 10 μmol/L, the inhibitory effect reached its maximum, no further inhibition was seen when the concentration of cimetidine increased to 100 μmol/L (Fig 1-A). At this time, the increase in HR was still significant compared to the data before challenge. The augmentation of dP/dt_{max} was remarkably suppressed in the presence of cimetidine at the concentration of 3 μmol/L.

Effects of cimetidine on the increase in HR and dP/dt_{max} caused by exogenous histamine in sensitized heart Bolus injection of histamine 5 μg increased HR by 18.9% ($P<0.01$) and dP/dt_{max} by 112.0% ($P<0.01$). HR increased less (Fig 2-A,

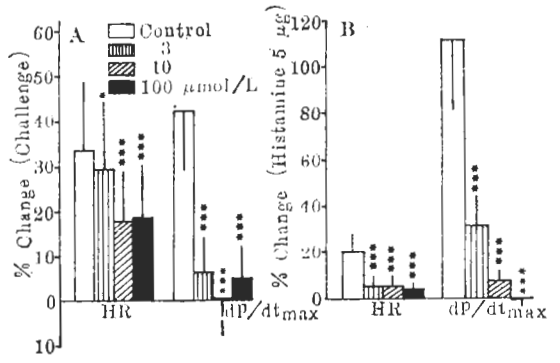

Fig 1. The changes of heart rate (HR) and dP/dt_{max} in augmentation phase of cardiac anaphylaxis (A) and after administration of histamine 5 μg (B) in the presence of cimetidine (n = 5-7). $\bar{x}\pm$ SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control (n = 10).

$P<0.05$) and dP/dt_{max} increased more (Fig 2-B, $P<0.01$) compared with those in the augmentation phase of cardiac anaphylaxis. Cimetidine significantly inhibited the increase in HR and dP/dt_{max} elicited by exogenous histamine (Fig 1-B). The enhancement of HR elicited by 5 μg exogenous histamine was inhibited by cimetidine more than that elicited in cardiac anaphylaxis (Fig 2 A, $P<0.01$), however, no difference with respect to the inhibitory effect on the augmentation of dP/dt_{max} between cardiac anaphylaxis and exogenous histamine was observed (Fig 2 B).

Effect of cimetidine on HR and dP/dt_{max} for histamine in normal isolated working guinea pig heart When observing the effects of a single dose of histamine, it was found that the increase in dP/dt_{max} reached its maximum 2 min after histamine injection, while the HR reached a maximum at 5 min. In the absence of H_2 receptor antagonist, the dose-response curve of dP/dt_{max} reached its peak with histamine 3 μmol/L. The increment began to decrease at histamine 10 μmol/L, however, the dose-response curve for HR did not show this pattern as it was still increasing at histamine 30 μmol/L. As a

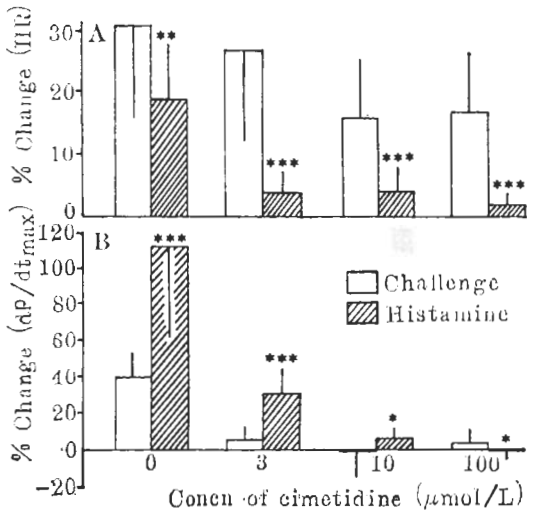

Fig 2. The changes of HR and dP/dt_{max} after histamine 5 μg injection (n = 10) in the presence of cimetidine (n = 5-7), $\bar{x}\pm$SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* the augmentation phase in cardiac anaphylaxis (n = 10).

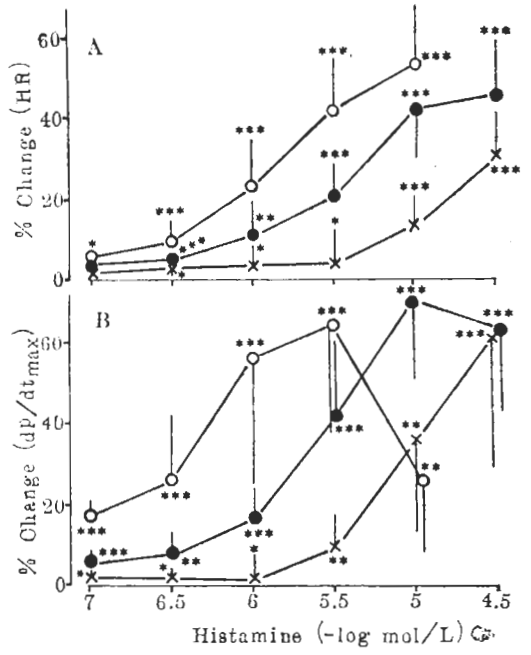

Fig 3. Effect of cimetidine on HR (A) and dP/dt_{max} (B) in normal isolated working guinea pig hearts. Concentration of cimetidine (●) 3 μmol/L, (×) 10 μmol/L, (○) histamine. n = 5, $\bar{x}\pm$SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* before histamine administration.

function of dose for both HR and dP/dt_{max}, dose-response curves for histamine were shifted in parallel to the right in the presence of cimetidine (Fig 3). No dissociation of the inhibitory effect of cimetidine on HR and dP/dt_{max} was observed.

Discussion

In the Langendorff heart preparation the increase in cardiac contraction and heart rate in the augmentation phase of cardiac anaphylaxis was mediated by histamine H_2 receptors and abolished by H_2 receptor antagonists[1]. The dissociation of the inhibitory effect of cimetidine on inotropic and chronotropic action has not been reported. Our results obtained from isolated working heart show that cimetidine abolished the increase in cardiac contraction, but did not completely inhibit the enhancement of HR in cardiac anaphylaxis. Although there is a concentration gradient of histamine content in guinea pig heart from the right atrium to left ventricle[4], the local concentration of histamine released into sinus node during cardiac anaphylaxis was much higher than that in myocardial cells of the left ventricle, however, this fact connot explain why the inhibition of HR did not increase when the cimetidine dose was increased. In our experiments, 5 μg of histamine was administered into the hearts by a bolus injection for comparison. It was found that the HR was increased by exogenous histamine by only about two third as much, while the dP/dt_{max} was increased by nearly 3 times as much as that by the challenge. As already shown in the experiments, the dissociation was not associated with sensitization, since no dissociation of the cimetidine effect on HR and dP/dt_{max} was observed in normal guinea pig hearts. A possible explanation is that in addition to histamine, some other substances such as LTs, PGs and PAF (platelet-activating factor) are concomitantly released in cardiac anaphy-

laxis which mediated positive chronotropic action on one hand, while on the other hand reduced coronary flow by their potent vasoconstrictive action, hence the remarkable decrease in cardiac contractility[5,6].

The existance of an H_2 receptor subtype may be another possibility. As observed in the experiments, the amount of time for the positive inotropic and chronotropic action to reach their maximum is different after the administration of histamine with dP/dt_{max} usually reaching its peak at about 2 min, while HR at about 5 min. Also, as seen in Fig 3, as the dose of histamine increased to 10 μmol/L, the increment of dP/dt_{max} declined, producing a bell-shaped curve. This is because at the maximum point of dose-response curve, a negative inotropic effect may appear as further doses of histamine are added[7], however, the increment of HR is not reduced. The facts suggest that the H_2 receptors mediating the positive inotropic and chronotropic effect had different susceptibilities, suggesting that the increase in automaticity of the sinus node and cardiac contraction may be mediated by different H_2 subtypes, and that the H_2 subtype mediating the positive inotropic action was more sensitive to cimetidine. The existance of an H_2 subtype in the right atrium has been reported[8].

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西咪替丁对心性变态反应中变力和变频作用影响的分离现象[1]

郭兆贵、丘　容　（湖南医科大学药理研究室，长沙 410078）

提要　本试验观察了西咪替丁对心性变态反应增强相及外源性组胺引起的心率和 dP/dt_{max} 变化的影响。西咪替丁能完全对抗心性变态反应增强相 dP/dt_{max} 的增加，但不能完全抑制心率的增快，而对组胺 5 μg 引起的致敏心脏的心率增快能予以取消。在西咪替丁存在情况下组胺对正常心脏的心率和 dP/dt_{max} 的量-效曲线均平行右移，且其对心率和 dP/dt_{max} 增加的抑制无分离现象。我们认为西咪替丁对心性变态反应中变力和变频作用影响的分离现象与某些能增快心率的介质释放有关。但组胺正性变力和变频作用的出现有时间差异，同时大剂量组胺（大于 3 μmol/L）不再引起 dP/dt_{max} 的增加，反使其下降，而心率的增快无此现象，提示心脏 H_2 亚型受体存在的可能性。

关键词　心性变态反应；离体工作心脏；组胺；西咪替丁；心肌收缩；心率

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