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Effect of histamine on isolated working guinea pig heart with left ventricular hypertrophy produced by pressure overload[1]

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Abstract Left ventricular hypertrophy in guinea pigs was produced by partial constriction of the ascending aorta. 65-70 d after surgery, the animals were sacrificed and the hearts were mounted on a working heart apparatus. Results showed that all parameters of cardiac function in the hypertrophied (HT) group were depressed. The dose-response (D-R) curves for histamine (H) in the HT group shifted leftward and upward as compared with the sham-operated (S) group. In the presence of pyrilamine (P), the D-R curves for H shifted to the left in the S group, but the curves shifted to the right in the HT group. In the presence of cimetidine (C), the D-R curves for H shifted downward and rightward in both groups. In contrast to H, the D-R curves for norepinephrine (NE) on LVP/HW and CBF/HW in the HT group shifted rightward and downward as compared with the S group. These results indicate that the sensitivity of H_2 receptors in hypertrophied heart was increased and that of β receptors was slightly decreased, suggesting a possible beneficial effect of H_2 receptor agonists in the treatment of certain types of cardiac failure, which are insensitive to catecholamine stimulation.

Key words histamine; cimetidine; pyrilamine; norepinephrine; heart enlargement; heart function tests

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Histamine is stored in large amounts in the mammalian heart. It can be released from bound storage sites, resulting in the alteration of cardiac performance[1]. The effects of H on the normal heart have been

extensively studied, however, little is known about the action and significance of H in cardiac dysfunction. Some facts have become available concerning this situation: 1) the concentration of H is increased in urine during acute myocardial infarction[2], 2) H can induce coronary spasm in patients with coronary artery atherosclerosis[3] and may be one of the candidates for the genesis of coronary vasospasm in patients with ischemic heart disease[4], 3) it also significantly augments the severity of the cardiac arrhythmias in the guinea pig heart with experimentally produced myocardial infarction[5]. Nevertheless, knowledge of the effect and characteristics of H on the hypertrophied heart are not known at present. In this study, we analyzed the effects of H and its antagonists on the isolated, hypertrophied working guinea pig heart. According to a report[6], the sensitivity of the cardiac β receptor was decreased while that of the H_2 receptor remained unaltered in the surviving non-ischemic myocardium after acute myocardial infarction. In cardiac hypertrophy, myocytes are in hypooxygenated circumstances because of the change in cardiac tissue structure. It is possible that the sensitivity of the cardiac β receptors was also changed. Hence, we also evaluated the effect of NE on the isolated hypertrophied working guinea pig heart in order to compare the different possible alterations between the β and H_2 receptor systems.

Methods

Establishment of left ventricular hypertrophy Male guinea pigs weighing 274±SD 14 g were anaesthetized with urethane (1–1.5 g/kg). An incision was made through the left 2 nd intercostal space. The chest wall was opened under artificial respiration and the pericardial sac in the region of the pulmonary artery was separated. A band 1.7 mm in diameter was placed on the proximal ascending aorta to produce a 70–75% constriction. Sham-operated animals underwent a similar procedure except for the immediate removal of the band[7]. 65–70 d after surgery, the animals were sacrificed by a heavy blow to the head and the hearts were removed and mounted on a working heart apparatus. The effects of H and its antagonists C and P and the adrenergic receptor agonist NE were evaluated.

Perfusion system and measurements The method of preparation of the isolated working heart and perfusion system were as described in references (8) and (9). Left ventricular pressure (LVP), dP/dt, left ventricular end diastolic pressure (EDP) and surface ECG were recorded by means of a 4 channel recorder. Coronary blood flow (CBF) and aortic blood flow (ABF) were collected and measured using a volumetric cylinder. Total cardiac output (T-CO) was obtained from the sum of CBF and ABF. CBF, ABF, T-CO and LVP were expressed as per gram dry weight of heart tissue, the heart tissue being dried in an oven at 84℃ for a period of 24 h.

The experiments were performed and compared between the HT and S groups. The heart preparations were equilibrated in the perfusion apparatus for at least 30 min until all physiological parameters attained stable values. Experiments were routinely completed within a further 50 min period.

Effects of histamine and norepinephrine H and NE ranging from 30 nmol/L to 10 μmol/L were administered into the perfusion system to achieve the desired concentrations. The incremental changes in the parameters were measured from control values. Semilogarithmic D-R curves for each agonist were obtained in separate preparations.

Effects of histamine receptor antagonists P (1 μmol/L) and C (3 μmol/L) were added to the perfusion system separately 5

min before the administration of H. H doses were given as described above. The D-R curves for H were obtained separately in the presence of P or C.

Data analysis Statistical analysis of the effects of agonists on the HT and S groups was carried out by the *t*-test. Significant shifts in the D-R curves between the two groups were determined by analysis of covariance. The effects of H in the presence of antagonists were compared with the effect of H alone in the same group. All data were processed by an IBM personal computer.

Drugs histamine dihydrochloride, pyrilamine maleate, cimetidine and norepinephrine were obtained from Sigma Company (St Louis, USA). All solutions were freshly prepared in 0.9% NaCl solution. Subsequent dilutions were made with perfusion medium.

Results

Cardiac hypertrophy 65-70 d after surgery, when the animal hearts were taken out for perfusion, the final body weights of the HT and S groups were similar (533 $\pm$9 *vs* 508$\pm$18 g, $P>0.05$). Constriction of the ascending aorta produced a 45.4% increase in LV weight/body weight in the HT group as compared with the S group (0.48$\pm$0.06 *vs* 0.33$\pm$0.03, $P<0.01$)[7].

Basal cardiac performance As shown in Tab 1, all parameters of cardiac function in the HT group were depressed as compared with the S group. For instance, the ABF/HW in group HT decreased 63% when compared with group S. This indicated depressed cardiac function in the hypertrophied hearts.

Effect of histamine on the isolated working heart H over the dose range of 30 nmol/L to 1 μmol/L produced dose-dependent increases in all measured parameters in both groups S and HT (Fig 1). LVP/HW, ABF/HW, CBF/HW, T-CO/HW

Tab 1. Cardiac functions of isolated working guinea pig hearts at basic state in sham-operated and hypertrophied groups. $\bar{x}\pm SD$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$

Parameter	Sham-operated (n = 5)	Hyper-trophied (n = 9)	Change (%)
HR (bpm)	228$\pm$18	189$\pm$9***	-17.1
LVP/HW (kPa/g)	64$\pm$12	40$\pm$7***	-37.5
$+dP/dt_{max}$ (kPa/s)	293$\pm$36	229$\pm$37***	-21.8
$-dP/dt_{max}$ (kPa/s)	195$\pm$54	138$\pm$27**	-29.2
ABF/HW (ml/g)	266$\pm$19	98$\pm$42***	-63.2
T-CO/HW (ml/g)	332$\pm$35	142$\pm$43***	-57.5
CBF/HW (ml/g)	66$\pm$7	43$\pm$9***	-33.3
EDP (kPa)	0.86$\pm$0.12	1.49$\pm$0.30***	73.2

LVP: Left ventricular pressure; ABF: Aortic blood flow; T-CO: Total cardiac output; CBF: Coronary blood flow; EDP: End diastolic pressure.

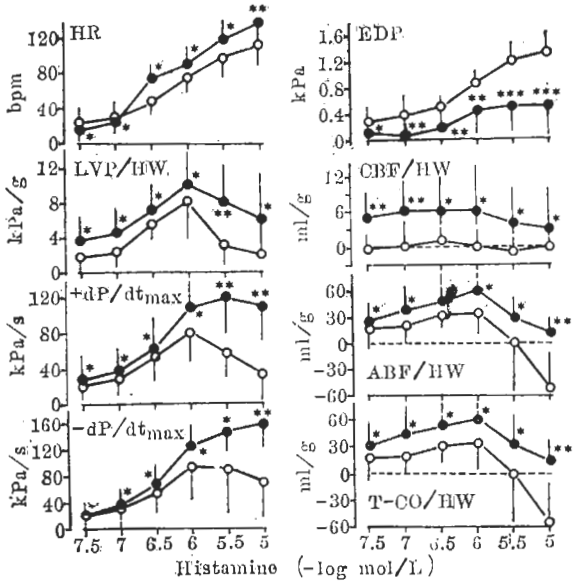

Fig 1. Dose-response curves for histamine. Open circle: sham-operated groups (n = 5), solid circle: hypertrophied groups (n = 9), $\bar{x}\pm SD$, $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$

in both groups and $\pm dP/dt_{max}$ in group S decreased gradually when the H dose exceeded 1 μmol/L. The D-R curves for H on all parameters in group HT shifted leftward and upward as compared with group S with the exception of EDP which shifted in the opposite direction.

Effect of histamine in the presence of

antagonists Antagonists P or C used alone in this study did not change the cardiac performance. In the presence of P, the D–R curves for H on $+dP/dt_{max}$ and LVP/HW in the S group shifted leftward and upward as compared with H alone. A similar tendency for $-dP/dt_{max}$ was also observed, but the D–R curves for $-dP/dt_{max}$ and LVP/HW in the HT group shifted to the right as compared with H alone. There was no significant displacement in $+dP/dt_{max}$ (Fig 2).

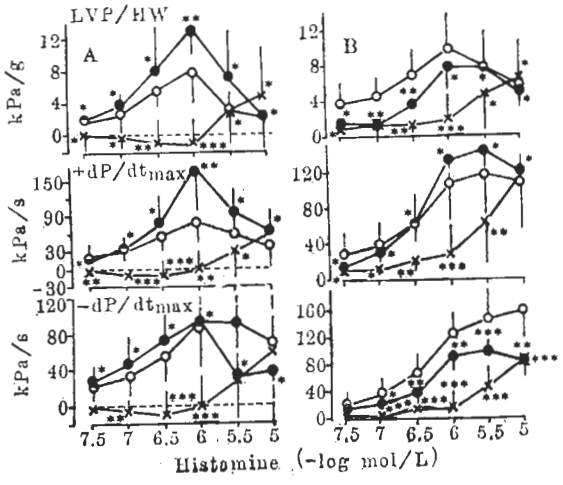

Fig 2. Dose-response curves for histamine alone (open circle, n = 9) and in the presence of pyrilamine 1 μmol/L (solid circle, n = 5) or cimetidine 3 μmol/L (cross, n = 6) in sham-operated groups (A) and hypertrophied groups (B). $\bar{x}\pm$SD. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* histamine alone.

C 3 μmol/L antagonized the effect of H on all parameters and produced a displacement of the D–R curves to the right in comparison with the effect of H alone as shown in Fig 2. A slightly negative inotropic effect was unmasked in group S when H doses ranged from 30 nmol/L to 1 μmol/L as reflected by $\pm dP/dt_{max}$ and LVP/HW. At greater concentrations, the negative inotropic effect became less and eventually positive (Fig 2).

The effect of norepinephrine on isolated working heart Like H, NE also produced dose-dependent increases in all measured parameters of cardiac function in both the HT and S groups. When the concentrations of NE exceeded 1 μmol/L, diminishment of LVP/HW, ABF/HW and T-CO/HW were observed. The D–R curves for HR, dP/dt_{max} and ABF/HW in the HT and S groups were similar, while CBF/HW and EDP shifted rightward and downward in group HT. When the concentrations were more than 1 μmol/L, the LVP/HW was also shifted downward (Fig 3).

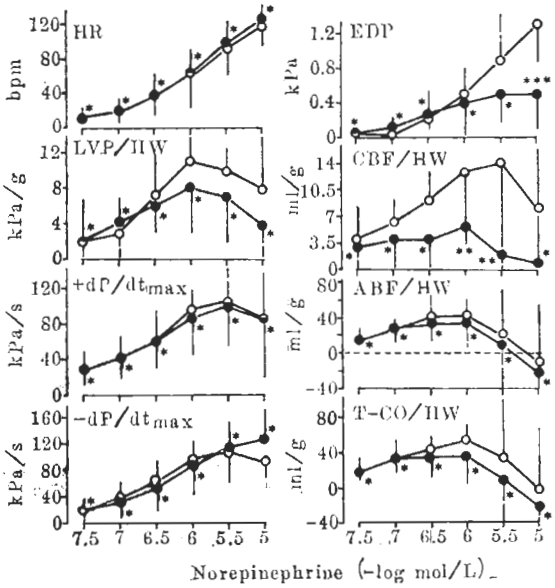

Fig 3. Dose-response curves for norepinephrine. Open circle: sham-operated groups (n = 5), solid circle: hypertrophied groups (n = 9). $\bar{x}\pm$SD. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$

Discussion

Complicated and even contradictory concepts as to whether cardiac function in hypertrophied heart is augmented, depressed or unchanged exist[10-12]. We found that the cardiac functions in HT hearts were depressed. This depression not only involved myocardial mechanical properties, but also cardiac pump function. Because the working heart is an energy consuming and work performing preparation, the results obtained from such a preparation are more informative and much closer to the clinical

situation than are those from a single muscle preparation.

H over the dose range of 30 nmol/L to 1 μmol/L produced dose-dependent augmentations in all measured parameters of cardiac function. The increases in sinus rate and contractility are in agreement with previous studies in which a variety of normal isolated guinea pig heart preparations were used[13]. However, when H concentrations were larger than 1 μmol/L, attenuations in LVP/HW, ABF/HW, T-CO/HW and CBF/HW were observed in both the HT and S groups, and depressions of $\pm dP/dt_{max}$ in S but not in the HT group were also observed. These results have not been reported so far. Cardiac pump function could be altered by rapid heart rate, but the decrease in $\pm dP/dt_{max}$ can not be merely explained by an increase in HR. Using a similar apparatus and preparations, Flynn[14] found that dP/dt_{max} was independent of the frequencies induced by electrical pacing. In this study, $\pm dP/dt_{max}$ continued to increase in the HT group even when the H dose was as high as 10 μmol/L, a dose at which the heart rate achieved 330 bpm. It is possible that decreased sensitivity to high H concentrations in group S was due to rapid desensitization of the H_2 receptors. No such desensitization occurred in group HT.

Although the response for $\pm dP/dt_{max}$ to low H doses (below 1 μmol/L) was similar for the groups HT and S, the response to high H doses was augmented in group HT. This result has not yet been reported, and further studies concerning the detailed mechanisms are needed. Baumann *et al*[6] found the sensitivity of H_2 receptors to impromidine was not altered while the sensitivity of β receptors to catecholamine was attenuated in the surviving non-ischemic myocardium. They observed that this attenuated response of β receptors was due to the diminished number and affinity of the receptors. In contrast, the augmented response to H in hypertrophied hearts found in this study may be attributed to the increased number or affinity of H_2 receptors.

P shifted the D-R curves for H on dP/dt_{max} and LVP/HW in group S upwards and to the left. Using preparations of human pectinate muscles, Guo *et al*[15] reported that P could shift the H D-R curves leftward and upward, suggesting that H_1 receptors exist in human atrium muscles. However, from the intact heart level, there has been no report suggesting the presence of H_1 receptors in the left ventricle. Our results have shown that in isolated working guinea pig heart, specifically the left ventricle, H_1 receptors also exist. In the presence of P, the H_1 mediated negative effect was abolished and the positive inotropic effect of H became even stronger. However, the same was not true in group HT, since H produced a depression in $-dP/dt_{max}$ and LVP/HW. The mechanism is not known at present.

C antagonized the effects of H on all measured parameters in both groups, indicating that the positive chronotropic and inotropic effects of H are due to an interaction with H_2 receptors. These results are in agreement with previous studies. It should be noted that in the presence of C, H could unmask a negative effect on contractility in group S, indicating the existance of an H_1 receptor mechanism in the isolated working guinea pig heart.

In conclusion, our results demonstrate that although the myocardial mass was increased as an adaptation to sustained overload in hypertrophied hearts, cardiac performance of the hypertrophied hearts decreased. In addition, the sensitivities of the hypertrophied hearts to β and H_2 receptor stimulation were also changed. The response to NE was somewhat decreased, while the response to H stimulation was

increased, especially when the H doses exceeded 1 μmol/L. This indicates an enhanced H_2 receptor sensitivity in hypertrophied hearts. These different alterations of sensitivities to β and H_2 receptor stimulation in hypertrophied hearts suggest a possible beneficial effect of H_2 agonists in the treatment of certain types of cardiac failure which may be insensitive to catecholamine stimulation.

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组胺对豚鼠左室压力性肥厚离体工作心脏的影响[1]

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提要 部分狭窄豚鼠升主动脉造成左室肥厚，术后 65-70 d 作离体工作心脏灌流，观察肥厚组基础状态下心功能及对组胺、吡拉明、西咪替丁和去甲肾上腺素的反应性与假手术组有无差别. 结果显示，基础状态下肥厚组心功能较假手术组为低；肥厚组组胺量-效曲线较假手术组左上移位；吡拉明使假手术组组胺量-效曲线左上移位，使肥厚组的量-效曲线右下移位；西咪替丁使两组所有组胺量-效曲线右下移位，结果表明，肥厚组 H_2 受体的敏感性较假手术组有所增强，而 β 受体的敏感性则有所减弱. 提示 H_2 受体激动剂可能用于某些不敏感于儿茶酚胺的心衰的治疗.

关键词 组胺；西咪替丁；吡拉明；去甲肾上腺素；心脏扩大；心脏功能试验

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