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

Luo Wei-sheng, Guo Zhao-Gui
(Research Section of Pharmacology, Hu-nan Medical University, Changsha 410078)

Abstract Left ventricular hypertrophy in guinea pigs was produced by a single 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 
H2 receptors in hypertrophied heart was increased and that of β receptors was slightly decreased, suggesting a possible beneficial effect of H2 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

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. 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 be-

come available concerning this situation: 1) the concentration of H is increased in urine during acute myocardial infarction[11]; 2) H can induce coronary spasm in patients with coronary artery atherosclerosis[13] and may be one of the candidates for the genesis of coronary vasospasm in patients with ischae-

mic heart disease[11]; 3) it also significantly augments the severity of the cardiac arrhythmias in the guinea pig heart with experi-

mentally produced myocardial infarction[15]. 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, hypertro-

phied working guinea pig heart. According to a report[14], the sensitivity of the cardiac β receptor was decreased while that of the H₂ receptor remained unaltered in the surviving non-ischemic myocardium after acute myocardial infarction. In cardiac hypertrophy, myocytes are in hypoxo-

genous 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 H₂ receptor systems.

Methods

Establishment of left ventricular hypertrophy Male guinea pigs weighing 274 ± 50 g were anesthetized with urethane (1.5 g/kg). An incision was made through the left 2nd intercostal space. The chest 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[17]. After 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 adren-

ergeic 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 ml/hr. The heart was dried in an oven at 84°C for a period of 24 h.

The experiments were performed and compared between the HE and SHS 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 nmo/L to 10 μmol/L were administered into the perfusion system to achieve the desired concen-

trations. 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 antago-

nists 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 dichlorhydrate, pyrilamine maleate, cimetidine and norprenphrine 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 atrial hearts were taken out for perfusion, the final body weights of the HT and S groups were similar (53±3 vs 50±8 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 (1.48±0.06 vs 0.33±0.03, P<0.01) (1).

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham- operated</th>
<th>Hyper-</th>
<th>Change</th>
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<tr>
<td></td>
<td>(0±5)</td>
<td>hypertrophied</td>
<td>(%)</td>
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<tr>
<td>HR (bpm)</td>
<td>228±14</td>
<td>150±9**</td>
<td>-37.1</td>
</tr>
<tr>
<td>LVP/HW (kPa)</td>
<td>64±12</td>
<td>40±7***</td>
<td>-37.6</td>
</tr>
<tr>
<td>+ dp/dt max (kPa/s)</td>
<td>303±36</td>
<td>228±37***</td>
<td>-21.8</td>
</tr>
<tr>
<td>- dp/dt max (kPa/s)</td>
<td>191±14</td>
<td>138±17**</td>
<td>-26.9</td>
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<tr>
<td>ABF/HW (ml/g)</td>
<td>260±28</td>
<td>98±14**</td>
<td>-63.2</td>
</tr>
<tr>
<td>T-CO/HW (ml/g)</td>
<td>502±30</td>
<td>122±24**</td>
<td>-75.6</td>
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<tr>
<td>CBF/HW (ml/g)</td>
<td>66±7</td>
<td>45±6**</td>
<td>-31.8</td>
</tr>
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</table>

EDP (kPa) 0.46±0.12 1.49±1.4* 75.2

LVFP: 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). + dp/dt max, P<0.01; + dp/dt min, P<0.05; **P<0.05; ***P<0.01.

In both groups and + 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 to the right 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 $+dP/dt_{\text{max}}$ and LVP/HW in the S group shifted leftward and upward as compared with H alone. A similar tendency for $-dP/dt_{\text{max}}$ was also observed, but the D-R curves for $-dP/dt_{\text{max}}$ and LVP/HW in the HT group shifted to the right as compared with H alone. There was no significant displacement in $+dP/dt_{\text{max}}$ (Fig 2).

![Fig 2. Dose-response curves for histamine alone (open circle, n=5) and in the presence of pyrilamine 1 μmol/L (solid circle, n=5) or cimetidine 3 μmol/L (cross, n=5) in sham-operated groups (A) and hypertensive groups (B).](image1)

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 $+dP/dt_{\text{max}}$ 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, diminished LVP/HW, ABF/HW and T-OC/HW were observed. The D-R curves for HR, $dP/dt_{\text{max}}$, and LVP/HW in the HT and S groups were similar, while CHF/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 5. Dose-response curves for norepinephrine. Open circle: sham-operated groups (n=5), solid circle: hypertensive groups (n=5).](image2)

**Discussion**

Complicated and even contradictory concepts as to whether cardiac function in hypertrophied heart is augmented, depressed or unchanged exist\cite{ref1, ref2, ref3, ref4}. 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...
situations then are those from a single muscle preparation. However, over the dose range of 30 mmol/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[13,14]. However, when H concentrations were larger than 1 μmol/L, attenuations in LVP/HW, AFB/HW, T-CO/HW and GSP/HW were observed in both the HT and S groups. and depressions of ±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 ±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, ±dP/dt max continued to increase in the HT group even when the H dose was as high as 10 mmol/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 receptors. No such desensitization occurred in group HT.

Although the response for ±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. Brunnen et al[14] found the sensitivity of H receptors to imipramine 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 receptors. P shifted the D-K 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[14] reported that P could shift the H D-R curves leftward and upward, suggesting that H receptors exist in human atrial muscles. However, from the intact heart level, there has been no report suggesting the presence of H receptors in the left ventricle. Our results have shown that in isolated working guinea pig heart, specifically the left ventricle, H receptors also exist. In the presence of P, the H 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 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 existence of an H receptor mechanism in the isolated working guinea pig heart.

In conclusion, the results demonstrate that although the myocardiol 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 receptor stimulation were also changed. The response to NE was somewhat decreased, while the response to H stimulation was
increased, especially when the if doses exceeded 1 mmol/L. This induced an enhanced H2 receptor sensitivity in hypertrophied hearts. These different alterations of sensitivities to β and H2 receptor stimulation in hypertrophied hearts suggest a possible beneficial effect of H2 agonists in the treatment of certain types of cardiac failure which may be insensitive to cetohepamine stimulation.

References

Heart 1 1985; 101: 569