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Inotropic effect of histamine on papillary muscle of guinea pig with right ventricular hypertrophy[1]

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ABSTRACT The effects of histamine and its antagonists on guinea pig right ventricular papillary muscle rendered hypertrophy by chronic pulmonary artery constriction were observed. In the HT-I group (hypertrophy 10-15 d), the dose-response (D-R) curves of PT, $\pm dT/dt_{max}$ of histamine, compared with CTL-I (age-matched sham-operated group), shifted leftward and upward. In the HT-II group (hypertrophy 30-35 d), while the histamine dosages ranged 0.1-1 μmol/L the D-R curves only slightly changed from CTL-II, but remarkably shifted rightward and downward in high concentrations (3-30 μmol/L), showing an augmentation of response in the early stage and an attenuation of response in the late stage. The pattern of D-R curves of epinephrine was virtually similar to those of histamine. In the presence of cimetidine, these curves all parallelly shifted to the right; and the biphasic inotropism were still clearly shown.

KEY WORDS histamine; right ventricular hypertrophy; papillary muscles; myocardial contraction; epinephrine; pyrilamine; cimetidine

In addition to immunological factors, there are many nonimmunological factors such as cardiac ischemic damage, certain physico-chemical and biological factors can also stimulate the release of endogenous histamine. Therefore, the role of histamine in non-immunological heart diseases is being investigated with growing interest. Recent studies have indicated that histamine can elicit coronary spasm in humans, and possibly is one of the endogenous factors for angina pectoris[1], and post-ischemic arrhythmia[2]. Baumann *et al* observed that inotropic effects of isoproterenol were nearly abolished while the inotropic effects of histamine, impromidine and dimaprit were not impaired on the guinea pig heart with left ventricular infarction[3]. Although regional ischemia and hypoxia are associated with the process of myocardial hypertrophy[4], only few reports concerning the inotropic effect of histamine during ventricular hypertrophy are available[5]. The purpose of this study is to observe the inotropic effects of histamine on hypertrophied guinea pig right ventricular papillary muscles, and to determine whether the effects of histamine are influenced by H_1 and H_2 blockade. It has been reported[6,7] that during ventricular hypertrophy and heart failure there was reduction cardiac stores of norepinephrine concomitant with an increase of circulating catecholamine, mainly epinephrine released from medulla of adrenal glands, which played an important role for maintenance of cardiac function. Thus we also compared the inotropic effects of epinephrine with those of histamine on papillary muscles at various stages of hypertrophy.

MATERIALS AND METHODS

Preparation of the experimental model and grouping The model of right ventricular hypertrophy was established according to the method described by Roskoski[8] with modifications. Guinea pigs of either sex weighing 277 ± SD 13 g were anesthetized with urethane 1.0 g/kg ip, positive pressure respiration was maintained with a respirator. A left thoracostomy was performed through the 2nd intercostal space. A glass rod of 1.7 mm in diameter was placed in parallel

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to the pulmonary artery, which was isolated by blunt dissection. A ligature was made with a silk thread passing around both the pulmonary artery and the rod. Then the glass rod was withdrawn. This produced about 70% constriction of the pulmonary artery. At the completion of the operation 200 000 units of carbenicillin was injected sc for prevention of infection.

Experimental animals were divided into 4 groups: animals of 10–15 d after operation were denoted as hypertrophy I group (HT-I), 30–35 d-hypertrophy II group (HT-II), and their age-matched sham operated groups denoted as control I (CTL-I) and control II (CTL-II), respectively.

Evaluation of the experimental model Two indices were employed to assure the cardiac hypertrophy. 1) The slides of papillary muscle were stained with methylene blue and the papillary muscle fiber diameter (PD) was measured under microscope. 2) The extent of hypertrophy at the level of ventricular mass was expressed as the ratio of the wet weight of right ventricular free wall to the body weight (RV/BW). The ratio of left ventricle including septum to body weight (LV/BW) served as a control for any independent changes in body weight.

Perfusion medium and condition of experiment The right anterior papillary muscle was isolated and removed from the hypertrophied right ventricle, and placed in a 3-ml perfusion bath containing Tyrode's solution[15] which was saturated and continuously aerated with 95% O_2 and 5% CO_2 (pH = 7.40). The temperature was kept at 32℃ and P_{O_2} monitored and controlled in the range of 53.2–79.8 kPa by an oximeter (Model CY-4).

Adjustment of optimal stimulation voltage and optimal initial length (L_{max}) The isolated papillary muscle connected to a force-displacement transducer (TB-612 T, Nihon Kohden Corp) was stimulated by square wave pulses at a frequency of 30/min, pulse width 10 ms. The optimal stimulation voltage was adjusted by stepwise increasing the voltage from the threshold to the point that the developed tension reaches its maximum. The L_{max} was adjusted by stepwise increasing the initial length from the length producing minimum developed tension to the point that the developed tension reaches its maximum. The optimal stimulation voltage and L_{max} for each papillary muscle were maintained throughout the entire course of the experiment.

Parameters to be observed and measured The signals of semi-isometric contraction of the papillary muscle were displayed on a polygraph (RM-6000, Nihon Kohden Corp) via a carrier amplifier (AP-620 G) and a differentiator (ED-600 G) to record the curves of developed tension (DT) and its first derivative (dT/dt), the stimulation signals were synchronously recorded on the charts. The parameters measured and calculated from the curves were the peak developed tension per unit of cross section area, PT (g/mm^2), and $\pm dT/dt_{max}$ ($g/mm^2 \cdot s^{-1}$).

Experimental designs Each papillary muscle of the experimental group was treated independently as follows: (1) Histamine (H), the effects of each concentration, calculated in a cumulative way, was observed for 3 min. Starting from the minimal effective concentration, 5–7 concentrations were added to test the dose-response relation. (2) Pyrilamine-histamine (P-H), pyrilamine (mepyramine) in a concentration of 3 μmol/L was added for 5 min, then the dose-response relation of histamine was tested as described above. (3) Cimetidine-histamine (C-H), cimetidine in a concentration of 3 μmol/L was added to test the dose-response relation of histamine as described. (4) Epinephrine (E), dose-response relation was tested as described for histamine.

The dose-response curve of each parameter in terms of net increment was plotted against log concentration for comparison.

Tab 1. Morphological and functional changes in right ventricular hypertrophy. $\bar{x}\pm SD$. *$p>0.05$, **$p<0.05$, ***$p<0.01$

Parameter	CTL-I (n=7)	HT-I (n=9)	CTL-II (n=5)	HT-II (n=9)
BW(g)	307±31	283±19*	345±25	342±23*
PD(μm)†	8.9±1.3	11.2±1.9***	8.6±0.9	14.4±3.2***
RV/BW(mg/g)	0.55±0.09	0.68±0.10**	0.59±0.12	0.72±0.18*
LV/BW(mg/g)	2.0±0.4	2.09±0.21*	2.03±0.25	1.81±0.22*
PT(g/mm^2)	0.08±0.03	0.15±0.08**	0.14±0.09	0.13±0.07*
dT/dt_{max}($g/mm^2 \cdot s^{-1}$)	0.9±0.3	1.5±0.9*	1.0±0.6	1.2±0.7*

†PD calculated from 40 fibres of two papillary muscles in each group. CTL-I: control I group. HT-I: hypertrophy I group. CTL-II: control II group. HT-II: hypertrophy II group.

The significance of data was analysed by *t* test.

Histamine, cimetidine and pyrilamine were obtained from Sigma chemical Co. Epinephrine is the product of The Wu-xi Fourth Pharmaceutical Factory. (Batch №. 810402-2)

RESULTS AND DISCUSSION

Morphological and functional changes in right ventricular hypertrophy Two features can be figured out from Tab 1. 1) In the HT-I group the RV/BW and PD increased by 24 and 26%, respectively. In the HT-II group, although the increase in RV/BW (not significantly different from CTL-II) was quite similar to HT-I group by 22%, the increase in PD was remarkably larger than HT-I group by 67%. 2) As one of indices of the mechanical properties of the hypertrophied muscle before treated, the PT was higher in HT-I group than in its control group. The dT/dt_{max} in this group was slightly higher than that in CTL-I group (but $p>0.05$). This result was similar to Kerr's[9]. There were no obvious difference of PT and dT/dt_{max} in HT-II group as compared with CTL-II group. All these demonstrated the characteristics of the earlier and late stages of hypertrophy.

The inotropic effects of histamine as compared with epinephrine on hypertrophied papillary muscles Results are shown in Fig 1. In HT-I group the dose-response curves of PT and $-dT/dt_{max}$ for histamine shifted leftward and upward with E_{max} increased, while the curve of dT/dt_{max} shifted leftward. In HT-II group the curves of PT and ±

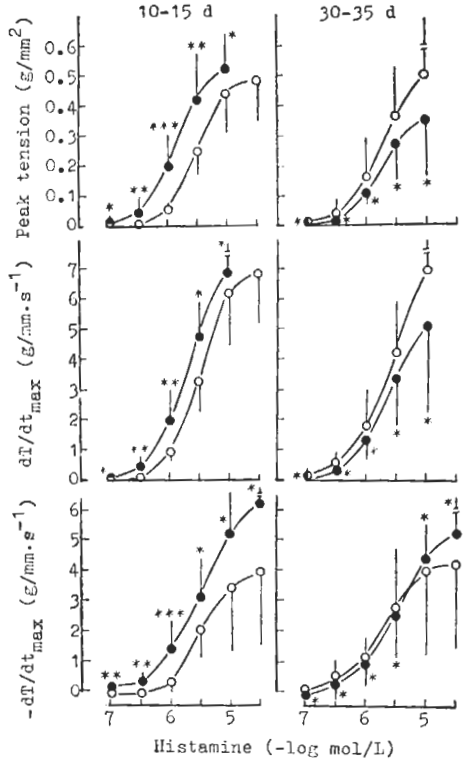

Fig 1. Effects of histamine on hypertrophied right ventricular papillary muscles. $\bar{x}\pm SD$.(○): sham-operated control, (●): hypertrophy. CTL-I: n=7; HT-I: n=9; CTL-II: n=5; HT-II: n=9. *$p>0.05$, **$p<0.05$, ***$p<0.01$

dT/dt_{max} for histamine with the dose range between 0.1–1 μmol/L only slightly changed from CTL–II, but in higher concentration (3 – 30 μmol/L) these curves shifted rightward and downward with the decrease in E_{max} remarkably. A biphasic inotropic changes of histamine effect was shown in different stages of hypertrophy: an augmentation of responses in the earlier stage and an at tenuation of responses in the late stage. The patterns of dose–response curves of PT and dT/dt_{max} of epinephrine were virtually similar to those of histamine (Fig 2), showing that myocardium of different stages of hypertrophy gave the similar response to these two inotropic agents. It was known that the inotropic effects of histamine and epinephrine

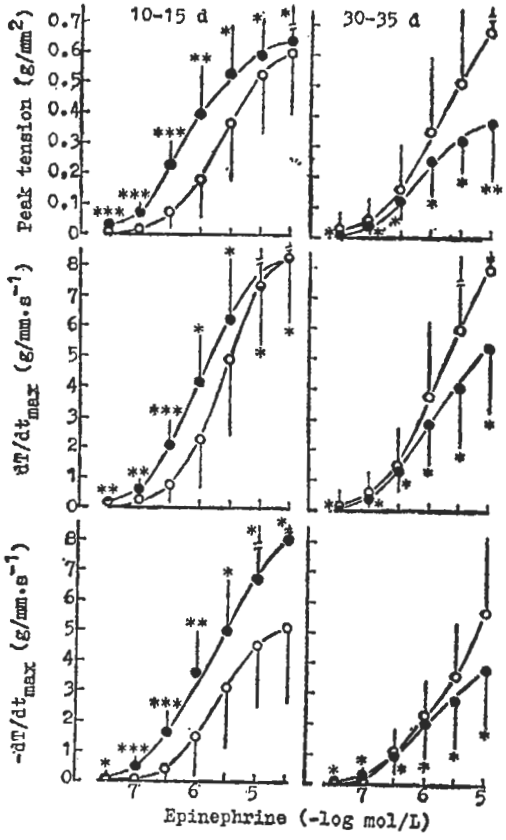

Fig 2. Effects of epinephrine on hypertrophied right ventricular papillary muscles. $\bar{x}\pm SD$. (○) sham–operated control, (●) hypertrophy. CTL-I n=7; HT-I n=9; CTL-II n=5; HT-II n=9. *p>0.05, **p<0.05, ***p<0.01

were mediated by H_2 receptors or adrenergic β–receptors. There were reports that in cardiac hypertrophy process the β–receptors changed in the number as well as the affinity. An increase in β–receptor density was shown by Karliner *et al*[10] on the hypertrophied heart induced by aortic constriction of guinea pigs; a decrease in β–receptor density in the late hypertrophy and heart failure were reported by other authors[11,12]. Some investigators considered that the change of β–receptor density was responsible for change in response to β–adrenergic stimulation in hypertrophic process[11,12]. It was inferred that the change in density of H_2 receptors might also be one of the possible underlying mechanism for the biphasic inotropic effect of histamine during different stages of ventricular hypertrophy. The quantitative changes in the intrinsic contractile state of each unit of myocardium during hypertrophy might also be another important factor, since the augmentation of isometric tension achieved by paired electric stimulation, increasing frequency of contraction and strophanthidin was reduced on papillary muscles from the hypertrophied right ventricles of cats[13]. It was postulated[14] that there were at least 2 separate adenyl cyclase systems in guinea pig hearts; one responsive to histamine, the other to norepinephrine. From the data obtained in this study it seems that during the ealier hypertrophy process the H_2 receptor–adenyl cyclase system possibly plays an important role for the maintenance of myocardial compensatory function.

Effects of histamine on hypertrophied right ventricular papillary muscle after H_1 or H_2 blockade Results were shown in Fig 3. In the presence of cimetidine 3 μmol/L, a negative inotropism caused by H_2 receptor blockade was seen at low concentrations (0.1–3 μmol/L) for all groups. The dose-response curve of PT of histamine shifted to the right at higher concentrations (3–100

μmol/L) in all groups. In HT-I group the E_{max} of response to histamine was still higher than that of the matched control, while in HT-II group the E_{max} of dose-response curves was still lower than that in CTL-II groups. In the presence of pyrilamine 3 μmol/L the curve in both hypertrophy groups were almost superimposable with those in matched groups. These facts indicated that after H_2 blockade the biphasic changes of response to histamine on hypertrophied muscles still remained, supporting that these changes were produced on the background of the change of the amount of receptors, probably not due to the changes of mechanical properties of muscle units themselves. It was reported that the inotropic response of human myocardium to histamine consists of 2 opposing components: a positive inotropism mediased by H_2 receptors and a negative inotropism mediated by H_1 receptors[15]. This study again proved that the negative inotropic response of hypertrophied papillary muscle was mediated by H_1 receptors.

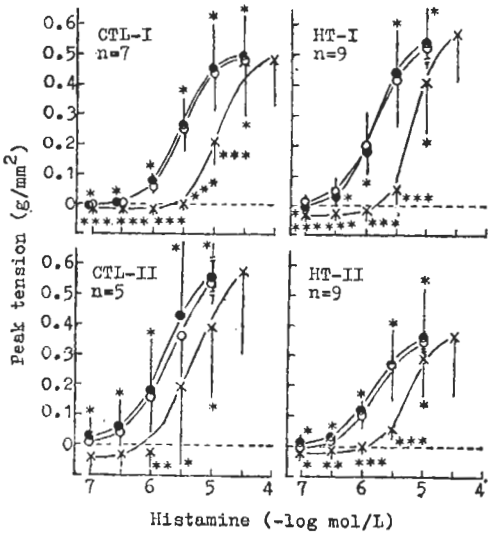

Fig 3. Effects of histamine on papillary muscles in the presence of pyrilamine or cimetidine $\bar{x}\pm SD$. (○) control; (●) pyrilamine 3 μmol/L; (×) cimetidine 3 μmol/L. *$p>0.05$, **$p<0.05$ *** $p<0.01$

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组胺对实验性豚鼠右室肥厚乳头状肌的变力作用[1]

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摘要　采用狭窄肺动脉造成的豚鼠右室心肌肥厚模型，观察了右室肥厚乳头状肌对组胺及其拮抗剂的变力反应，并与肾上腺素比较。形态学和组织学检查结果显示，心肌肥厚的早期(10-15 d)(HT-Ⅰ)与晚期(30-35 d)(HT-Ⅱ)存在不同的形态和力学特征。在 HT-I 组，组胺的 PT，dT/dt_{max} 量效曲线均左上移位，E_{max} 增高，在 HT-II 组，组胺 PT，dT/dt_{max} 量效曲线在低浓度(0.1-1 μmol/L) 时移位不明显，高浓度 (3-30 μmol/L)时明显右下移，E_{max} 降低，呈双相变化：早期加强，后期减弱。提示在肥厚晚期，心肌的实际储备能力降低，肾上腺素对右室肥厚乳头状肌变力作用的量效曲线变化与组胺相似。

在西咪替丁存在下，两假手术对照组 (CTL-I, CTL-II)组胺的 PT，dT/dT_{max} 量效曲线于低浓度 (1-3 μmol/L)时呈现负性变力作用，高浓度(10-100 μmol/L)时平行右移，与相应对照组比较，HT-1 组对组胺反应增强，HT-II 组对组胺反应减弱的现象依然存在。提示在不同肥厚时期，对组胺反应的差异，可能与 H_2 受体密度改变有关。

关键词　组胺；右室肥大；乳头状肌；心肌收缩；肾上腺素；美吡拉敏；西咪替丁

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