Effects of H₁-Receptor Stimulation on Coronary Arterial Diameter and Coronary Hemodynamics in Humans

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Effects of H₁-receptor stimulation on coronary arterial diameter and coronary hemodynamics were examined in 11 patients with angiographically normal coronary arteries and without variant angina or resting angina. Selective H₁-receptor stimulation was achieved by infusing histamine into the left coronary artery at a rate of 2.0 µg/min for 5 minutes after pretreatment with cimetidine (25 mg/kg). Plasma histamine concentration in the coronary sinus, coronary sinus blood flow, heart rate, and aortic pressure were measured before, during, and after the histamine infusion. Coronary arterial diameter was measured by cinevideodensitometric analysis of coronary arteriograms performed before and immediately after the histamine infusion. During the histamine infusion, plasma histamine concentration in the coronary sinus increased from 0.33±0.06 to 5.86±0.71 ng/ml (p<0.01); coronary sinus blood flow increased from 98±12 to 124±13 ml/min (p<0.01), and coronary vascular resistance decreased from 1,113±117 to 851±91 mm Hg·min/l (p<0.01). Heart rate and aortic pressure remained unchanged. The mean luminal diameters of the proximal, middle, and distal left anterior descending artery increased by 9.4±3.6% (p<0.05), 19.2±3.8% (p<0.001), and 31.5±5.6% (p<0.001), respectively, after the histamine infusion. The mean luminal diameters of the proximal, middle, and distal left circumflex artery increased by 15.2±3.6% (p<0.01), 17.5±5.2% (p<0.01), and 20.6±4.3% (p<0.001), respectively, after the histamine infusion. We conclude that histamine at the present dose dilates large coronary arteries as well as small coronary resistance vessels via H₁-receptor stimulation in patients with angiographically normal coronary arteries and without variant angina or resting angina. (Circulation 1990;81:65-71)

Coronary artery spasm has been shown to play an important role in the production of not only variant angina but also other forms of resting angina, some forms of exertional angina, and some forms of acute myocardial infarction. However, the precise mechanisms by which coronary artery spasm occurs still remain unknown.

Intravenous infusion of histamine after blockade of H₂-receptors by cimetidine or H₁-receptor stimulation induced coronary artery spasm in some patients with variant angina and in the miniature swine in which the coronary artery was denuded and a high cholesterol diet was fed. An autopsy case report of variant angina showed that the number of mast cells releasing histamine was increased in the coronary artery segment that had been involved in spasm. Thus, it has been suggested that histamine plays a role in the pathogenesis of coronary artery spasm.

Studies on isolated human coronary arteries have shown that H₁-receptor stimulation causes vasoconstriction while H₂-receptor stimulation causes relaxation. There is also a recent report showing that histamine causes relaxation at the lower concentrations (up to 5×10⁻⁷ M) and constriction at the higher concentrations in isolated human coronary arteries. However, there is no report on the response of normal human epicardial coronary arteries to histamine in vivo.

The present study was designed to examine the effects of H₁-receptor stimulation on human epicardial coronary arteries as well as on coronary hemo-
dynamics in patients with angiographically normal coronary arteries and without evidence of variant angina or resting angina.

Methods

Patient Group

We studied 21 patients (13 men and eight women; age, 20–68 years; mean age, 54 years) who underwent diagnostic catheterization and were proved to have normal coronary arteries and no evidence of myocardial ischemia. No patient had typical anginal pain at rest or on exertion. Maximal exercise stress testing according to Bruce’s standard protocol was negative in all patients. Ambulatory electrocardiographic monitoring and the hyperventilation test for provoking coronary spasm were also done in all patients and were negative for myocardial ischemia in all of them. Exercise myocardial scintigraphy with thallium 201 was done in five patients, and all of them showed normal myocardial perfusion. At the cardiac catheterization, intracoronary injection of acetylcholine into both the left and the right coronary artery was done in an attempt to provoke coronary spasm in all patients after the completion of this study. Neither chest pain nor ischemic ST segment changes appeared, and coronary arteriography showed no evidence of coronary spasm after this procedure in any of the patients. Thus, the patients included in this study were considered to have no evidence of myocardial ischemia, including variant angina or resting angina. All the patients had normal hemodynamic data and ejection fraction. Patients with allergy, chronic obstructive lung disease, peptic ulcer, and old myocardial infarction were excluded from the present study.

The patients were divided into the histamine group and the control group. The histamine group consisted of 11 patients (seven men and four women; mean age, 52 years). Ten of them had atypical chest pain, and the remaining patient had suffered from myocarditis. The control group consisted of 10 patients (six men and four women; mean age, 56 years). Seven patients had atypical chest pain, two patients hypertrophic cardiomyopathy, and one patient mild mitral regurgitation. All drugs were stopped for at least 3 days before the study. The study protocol was approved by the Kumamoto University Medical School Ethics Committee, and written informed consent was obtained from each patient.

Catheterization Procedures

The study was performed in the morning in the fasting state. A 7F thermodilution coronary blood flow catheter (model CCS-7U-90B, Webster, Altdena, California) was positioned in the coronary sinus via the right antecubital vein. 

Catheter position was determined by injection of a small volume of Urogratin (Schering AG, Berlin, Germany), and stable catheter position was confirmed by fluoroscopy during the procedure. A 6F Goodale-Lubin catheter (USCI, Billerica, Massachusetts) for blood sampling was inserted from the right subclavian vein and placed in the coronary sinus in the same way as mentioned above. Coronary arteriography was performed using the Sones technique, and the control coronary arteriograms of the left coronary artery in the right anterior oblique projection and of the right coronary artery in the left anterior oblique projection were taken. Relations between focal spot, patient, and height of image tube were kept constant. A tripolar electrode catheter (USCI) was inserted into the right ventricle apex via the femoral vein and connected to a temporary pacemaker set at a rate of 40–50 beats/min.

Study Protocol

In the histamine group, cimetidine, an H2-receptor antagonist, was administered before the study to perform selective H1-receptor stimulation: 10 mg/kg was given orally 1 hour before the intracoronary histamine infusion, and then 15 mg/kg was injected intravenously 5 minutes before the control arteriography. Ten minutes after control coronary arteriography, heparinized blood samples for histamine determination were collected from the coronary sinus and the femoral vein, and baseline measurements of heart rate, aortic pressure, and coronary sinus blood flow were done. Coronary sinus blood flow was determined by the injection of nonheparinized normal saline solution through the thermodilution catheter with a constant infusion pump at a rate of 36 ml/min and calculated using a Thermo Flow RF (Good Man, Altadena, California). 

After control blood sampling for histamine assay and baseline measurements of hemodynamic variables, histamine, dissolved in warmed normal saline (1.0 μg/ml), was infused into the left coronary artery at a rate of 2.0 μg/min through the Sones catheter positioned in the left coronary ostium. The infusion was continued for 5 minutes.

In the control group, warmed normal saline was infused into the left coronary artery at the same rate and duration to examine the effect of saline itself on coronary diameter and hemodynamic parameters.

The position of the tip of the Sones catheter was confirmed frequently by fluoroscopy during the histamine or saline infusion. Arterial blood pressure and three leads (I, aVF, and V3) of the electrocardiogram were constantly monitored during the histamine or saline infusion, and a standard 12-lead electrocardiogram was obtained at appropriate intervals with the use of radiolucent carbon electrodes as the chest lead electrodes.

In the histamine group, measurements of heart rate and aortic pressure were performed every minute during the histamine infusion and 2 and 5 minutes after termination of the infusion. Coronary sinus blood flow was measured 5 minutes after initiation of the histamine infusion and 5 minutes after termination of the infusion. Blood sampling from the coronary sinus and the femoral vein were performed 20
seconds before each measurement of hemodynamic variables. In the control group, coronary sinus blood flow, heart rate, and aortic pressure were measured before and 5 minutes after initiation of the saline infusion. The arteriogram of the left coronary artery in the right anterior oblique projection was taken immediately after termination of the histamine or saline infusion. The histamine study protocol is shown diagrammatically in Figure 1.

**Calculation**

Coronary vascular resistance was calculated by the following formula: coronary vascular resistance (mm Hg · min/l) = mean aortic pressure × 1,000/coronary sinus blood flow.

**Angiographic Analysis**

Measurement of the luminal diameters of the left anterior descending artery and the left circumflex artery at the proximal, middle, and distal portions of each vessel was performed quantitatively using the cinevideodensitometric analysis system (model XR-70 coronary analyzer, Vanguard Instruments Corp., Melville, New York). This system has been validated in previous studies.14 15 Briefly, the 35-mm cine film was projected with a Vanguard projector (model XR-35), and a single cine frame was selected for analysis on the basis of clear visualization with optimal opacification of the coronary artery and without overlapping vessels at end diastole. The selected cine frame was projected on a 12-in. video screen with twofold magnification, and this image was analyzed by positioning regions of interest on either side of the catheter shaft and a segment of the coronary artery. Lines connecting the pairs of regions of interest were generated by the microprocessor, and videodensity values for the pixels delineated by these lines were measured five times and averaged. The portion of the catheter just proximal to the primary curve was used as a scaling device to determine absolute diameter. After the analysis a photograph (type 331, Polaroid Corp., Cambridge, Massachusetts) of this video image was taken.

The luminal diameter of each portion of the coronary artery was analyzed before and after the histamine or saline infusion at end diastole. In analyzing the arteriogram after the histamine or saline infusion, care was taken to select the same point where the analysis of the control arteriogram was performed. The arteries were analyzed in a blinded fashion by two physicians who were unaware of the identity of the patient or the study protocol. Analysis of intraobserver and interobserver variability for the measurement of diameter of the human coronary artery showed high reproducibility (r=0.99, SEE=0.12 mm, p<0.001, and r=0.98, SEE=0.16 mm, p<0.001, respectively).

**Histamine Determination**

Plasma histamine levels were determined by high-performance liquid chromatography using post column derivatization technique, which was partly based on the method of Shore et al.16 Briefly, histamine was extracted into n-butanol from plasma, which was then back-extracted into 0.1 M hydrochloric acid and injected into the LC-6A high-performance liquid chromatography system (Shimadzu, Kyoto, Japan) equipped with an RF-530 fluorescence monitor and a C-R3A data terminal (Shimadzu). The column used was the ISC-05/S0504 (50×4.0 mm internal diameter, Shimadzu). The mobile phase was 1 M sodium perchlorate in 100 mM Na edetate (pH 9.3) and was delivered isocratically at 0.5 ml/min at the column temperature of 70° C. After separation by ion-exchange column chromatography, on-line derivatization of histamine to a highly fluorescent compound with orthophthalaldehyde was performed. The fluorescence intensity was monitored at the emission wavelength of 440 nm with the excitation wavelength set at 360 nm. Histamine in human plasma could be determined without any interference of coexisting impurities. Values were expressed as nanograms per milliliter histamine base. Calibration curves were generated from histamine standards diluted in human plasma in each set of samples. The coefficient of variation of this method was calculated to be 4.0% at 1 ng/ml histamine in plasma in our laboratory.
Statistics

Differences of variables (plasma histamine levels and hemodynamic measurements) from baseline were tested for significance by one-way analysis of variance for repeated measures and the Bonferroni t test. A two-tailed paired Student’s t test was used in analysis of changes in the coronary arterial diameter by the histamine or saline infusion at each portion of the vessel and in analysis of changes in the hemodynamic variables by the saline infusion. Comparisons of the percent diameter changes by the histamine infusion at the three portions of the same artery were performed with one-way analysis of variance and the Bonferroni t test. Intraobserver and interobserver correlations were determined by the linear regression equation (the method of least squares). All values were expressed as mean ± SEM. A p value less than 0.05 was defined as statistically significant.

Results

Effects of Intracoronary Infusion of Saline

Normal saline infusion into the left coronary artery in 10 patients did not cause any significant changes in coronary sinus blood flow (from 113±12 to 113±11 ml/min), coronary vascular resistance (from 1,049±107 to 1,009±91 mm Hg · min/l), and rate-pressure product (from 11,813±1,046 to 11,947±1,097 beats/min · mm Hg). The infusion also did not cause any significant changes in the diameters of the proximal, middle, and distal left anterior descending artery (from 3.1±0.2 to 3.0±0.2 mm, from 1.9±0.2 to 1.9±0.2 mm, and from 1.4±0.1 to 1.4±0.1 mm, respectively) and the diameters of the proximal, middle, and distal left circumflex artery (from 2.6±0.1 to 2.6±0.1 mm, from 1.9±0.2 to 1.9±0.1 mm, and from 1.4±0.1 to 1.4±0.1 mm, respectively) in these patients.

Effects of H1-Receptor Stimulation on Systemic and Coronary Hemodynamics

Throughout the study there were neither subjective complaints nor complications with the intracoronary histamine infusion. No patient developed chest pain or ischemic ST-T changes on the electrocardiogram during and after the histamine infusion. Mean values of plasma histamine concentration and hemodynamic variables during the study are shown in Table 1.

Mean baseline plasma histamine concentrations in the coronary sinus and the femoral vein were 0.33±0.06 and 0.40±0.06 ng/ml, respectively. Two minutes after the histamine infusion, the histamine concentration in the coronary sinus increased significantly and reached the maximum concentration of 5.86±0.71 ng/ml 5 minutes after the infusion (p<0.01 vs. baseline). After termination of the infusion, the histamine concentration in the coronary sinus decreased rapidly and returned to the baseline level (0.37±0.07 ng/ml) 5 minutes after termination of the infusion. On the other hand, the mean plasma histamine level in the femoral vein remained unchanged during the histamine infusion.

Coronary sinus blood flow increased significantly from 98±12 to 124±13 ml/min (p<0.01) during the histamine infusion and returned to the baseline level 5 minutes after termination of the infusion. On the other hand, coronary vascular resistance significantly decreased from 1,113±117 to 851±91 mm Hg · min/l (p<0.01) during the infusion and returned to the baseline level 5 minutes after termination of the infusion.

No significant changes in heart rate, aortic pressure, and rate-pressure product were observed during the intracoronary histamine infusion.
Effects of H<sub>1</sub>-Receptor Stimulation on Coronary Arterial Diameter

The mean luminal diameters of the proximal, middle, and distal left anterior descending artery increased from 3.1±0.2 to 3.4±0.3 mm or by 9.4±3.6% (p<0.05), from 2.0±0.1 to 2.4±0.1 mm or by 19.2±3.8% (p<0.001), and from 1.6±0.1 to 2.0±0.2 mm or by 31.5±5.6% (p<0.001), respectively, after the histamine infusion. The mean luminal diameters of the proximal, middle, and distal left circumflex artery increased from 3.0±0.2 to 3.4±0.2 mm or by 15.2±3.6% (p<0.01), from 2.2±0.2 to 2.5±0.1 mm or by 17.5±5.2% (p<0.01), and from 1.4±0.1 to 1.6±0.1 mm or by 20.6±4.3% (p<0.001), respectively, after the histamine infusion.

The response of the coronary artery to the histamine infusion in each patient is summarized in Figure 2 as the percent diameter change from the control. Both the intraobserver and interobserver variability with respect to percent change was low (r=0.98, SEE=4.7%, p<0.001, and r=0.96, SEE=5.1%, p<0.001, respectively). Although the left anterior descending artery constricted at the proximal portion by 17% in one patient and showed no change at the middle portion in two patients, the artery dilated at all the portions in the other patients after the histamine infusion. The left circumflex artery dilated at all the portions in all patients except one whose artery showed no change in all the portions. In the left anterior descending artery, the dilation in response to the histamine infusion was significantly greater in the distal portion than in the proximal portion (31.5±5.6% vs. 9.4±3.6%, p<0.01). The same tendency was also observed in the left circumflex artery although this was not statistically significant. A representative case is shown in Figure 3.

Discussion

The constant infusion of histamine into the left coronary artery at a rate of 2.0 μg/min increased the plasma histamine concentration in the coronary sinus to a mean of 5.86 ng/ml without changing the histamine concentration in the femoral vein. In this study, we performed the histamine assay using high-performance liquid chromatography with fluorescence detection, which has been validated and widely accepted as the standard method. The baseline plasma histamine levels in the coronary sinus and the femoral vein in the present patients were consistent with the plasma histamine levels determined with the

Figure 2. Percent changes in coronary arterial diameter by histamine infusion at proximal (Prox), middle (Mid), and distal (Dis) portions of the left anterior descending artery (LAD) and the left circumflex artery (LCX) in 11 study patients. Each artery in each patient is represented by different symbols, and proximal, middle, and distal portions of the same artery are joined by lines. The same symbol used in the separate panels indicates the same patient. *p<0.05, **p<0.01, ***p<0.001 (vs. control level).

Figure 3. Arteriograms of left coronary artery before (left) and after (right) histamine infusion in a 36-year-old man symbolized by ♂ in Figure 2. The artery dilated after the histamine infusion.
use of radioimmunoassays reported recently.\textsuperscript{21,22} Thus, the method for the histamine assay in this study was considered to be reliable.

The infusion of histamine significantly increased coronary arterial diameter and coronary sinus blood flow and significantly decreased coronary vascular resistance without changing heart rate, aortic pressure, and rate-pressure product. Because intracoronary infusion of saline per se did not affect coronary arterial diameter, coronary sinus blood flow, coronary vascular resistance, and rate-pressure product, the changes in coronary arterial diameter and coronary hemodynamics observed after the histamine infusion were induced by the coronary H\textsubscript{1}-receptor stimulation. When histamine is administered intravenously, a sympathetic response to the acute fall in arterial pressure, or a direct histamine effect on adrenal medulla, or both may cause the increase in plasma levels of catecholamines.\textsuperscript{5} On the other hand, the dose of cimetidine used in the present study was considered to be sufficient to produce cardiovascular H\textsubscript{2}-receptor blockade.\textsuperscript{4,23} Thus, the influences of both adrenergic and histamine H\textsubscript{2}-receptor systems were excluded, and the direct effects of H\textsubscript{1}-receptor stimulation on coronary circulation could be observed in this study.

**Effects of H\textsubscript{1}-Receptor Stimulation on Coronary Hemodynamics**

This study showed that the selective H\textsubscript{1}-receptor stimulation with a relatively low dose of histamine induced an increase in coronary sinus blood flow and a decrease in coronary vascular resistance. Since heart rate and arterial pressure remained unchanged during the histamine infusion, it was considered that histamine at the present dose dilated small coronary resistance vessels via H\textsubscript{1}-receptor stimulation without affecting myocardial oxygen consumption. This observation is consistent with the results of the recent study by Vigorito et al\textsuperscript{24} who reported that an intracoronary bolus injection of 4 \( \mu \)g histamine after H\textsubscript{2}-receptor blockade by cimetidine increased coronary sinus blood flow and decreased coronary vascular resistance with minor changes in heart rate and mean arterial pressure immediately after the injection. Constant histamine infusion into the left coronary artery in the present study is considered to show the effects of H\textsubscript{1}-receptor stimulation more precisely than those observed in Vigorito’s study. Moreover, we measured plasma histamine levels in both the coronary sinus and femoral vein.

**Effects of H\textsubscript{1}-Receptor Stimulation on Coronary Arterial Diameter**

There has been no study on the effects of selective H\textsubscript{1}-receptor stimulation on the human epicardial coronary arterial diameter in vivo. Our results clearly showed that the selective H\textsubscript{1}-receptor stimulation in patients with angiographically normal coronary arteries and without variant angina or resting angina produced dilatation of epicardial coronary arteries.

Ginsburg and his coworkers\textsuperscript{8} showed that histamine produced vasoconstriction of isolated human epicardial coronary arteries and that this contractile response to histamine was mediated by H\textsubscript{1}-receptors, while the stimulation of H\textsubscript{2}-receptors caused vasodilatation. Recently, Toda\textsuperscript{8} reported that histamine appeared to act on H\textsubscript{1}-receptors in the endothelium of isolated human coronary arteries and to release the relaxing factor from the endothelium. Thus, histamine produced a relaxation of the artery via release of the relaxing factor at the lower concentrations (up to 5\( \times \)10\textsuperscript{-7} M) and a vasoconstriction at the higher concentrations. Because the histamine infusion in the present study resulted in the maximum plasma histamine concentration of 5.86 ng/ml (0.5\( \times \)10\textsuperscript{-7} M) in the coronary sinus, the histamine level in our in vivo study is considered to be lower than the threshold stimulus for vasoconstriction but sufficient to induce endothelium-dependent relaxation. This finding seems to explain the mechanism by which H\textsubscript{1}-receptor stimulation in the present study caused relaxation of the epicardial coronary arteries.

Using isolated human epicardial coronary arteries, Ginsburg et al\textsuperscript{25} has shown that the contractile response to histamine (10\textsuperscript{-6} M to 10\textsuperscript{-4} M) is decremental along the length of the artery. Another recent report has suggested that both the direct (H\textsubscript{1}) and endothelial (H\textsubscript{2}) relaxant actions are more potent in the distal portion than in the proximal portion of the coronary artery in the range of histamine concentration of 10\textsuperscript{-5} M to 10\textsuperscript{-4} M.\textsuperscript{26} In our study, the alteration in the luminal diameter in response to histamine was significantly greater in the distal portion than in the proximal portion of the left anterior descending artery, and the same tendency was also observed in the left circumflex artery. Thus, the relaxation of the coronary artery, particularly in the distal portion, in response to histamine was demonstrated in humans in vivo.

**Clinical Implications**

Our study demonstrated that the selective H\textsubscript{1}-receptor stimulation with a low dose of histamine caused dilatation in both small coronary resistance vessels and large coronary arteries in patients with angiographically normal coronary arteries and without variant angina or resting angina. Ginsburg et al\textsuperscript{4} injected histamine intravenously at a rate of 1.0 \( \mu \)g/kg/min and reported histamine induced coronary spasm in some patients (33%) with variant angina. It has been reported that the intravenous infusion of histamine at the same rate is associated with an increase in the plasma histamine level to 6 ng/ml,\textsuperscript{27} which is almost the same level as attained in the coronary sinus during the intracoronary histamine infusion in the present study. Thus, the coronary arteries of patients with variant angina may have different responses to histamine from those of patients without this syndrome. This finding may provide an important clue for the elucidation of the pathogenesis of coronary spasm.
References


Key Words • histamine • coronary vessels
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