Hyperreactivity of Coronary Arterial Smooth Muscles in Response to Ergonovine from Rabbits with Hereditary Hyperlipidemia

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SUMMARY. This study was undertaken to examine the response to ergonovine, an agent used to provoke spastic constriction of large epicardial coronary arteries, to elucidate the responsible underlying mechanism, and to determine the impact of endogenous hyperlipidemia on contractile properties of isolated vessels from different beds. The isolated arteries from both control and Watanabe hereditary hyperlipidemic rabbits (WHHL rabbits) were suspended for recording isometric force in oxygenated Krebs buffer and exposed to agonists and antagonists. In atherosclerotic aortas from WHHL rabbits, the concentration-response relations for ergonovine and serotonin exhibited a marked leftward shift with significantly depressed constrictor threshold concentration and lowered one-half maximally effective concentration values. In coronary arteries with no atherosclerotic lesions detectable macroscopically from WHHL rabbits, the concentration-response relations showed a leftward shift for ergonovine but not for serotonin. Coronary contraction evoked by ergonovine was remarkably inhibited by 0.1 μM cyproheptadine and 0.3 μM methysergide, serotonergic antagonists, in both groups. α-Adrenergic blockade with 0.1 μM prazosin was effective in inhibiting ergonovine-induced contraction of aortas from control rabbits, but not that of atherosclerotic ones. The constrictor response to ergonovine of atherosclerotic aortas was inhibited by cyproheptadine. The responsiveness to ergonovine of both carotid and femoral arteries from WHHL rabbits with no sclerotic lesions, which was suppressed by prazosin was not different from that of control rabbits. In contrast, the concentration-response relations for phenylephrine in the four different types of arteries did not differ appreciably between the two groups, and the constrictor responses to 20 mM KCl were virtually identical. Thus, aortas and coronary arteries exposed to endogenous hyperlipidemia appear to be hyperreactive to ergonovine mediated by a serotonergic mechanism. (Circ Res 53: 63-71, 1983)

SPASM of large coronary arteries appears to play an important role in eliciting myocardial ischemia (Maseri et al., 1979). However, the causes of physiologically inappropriate vasomotion are not yet clear. Pharmacological agents have been used diagnostically to provoke coronary arterial spasm in patients with suspected vasospasm (Yasue et al., 1974; Endo et al., 1976), and ergonovine maleate, an amine ergot alkaloid, has been advocated as a specific and potent agent for this purpose (Schroeder et al., 1977; Heupler et al., 1978; Curry et al., 1979). Spasm occurs not only in association with atherosclerotic lesions, but also in angiographically normal coronary arteries (Meller et al., 1976).

Since ergot alkaloids, such as ergotamine and ergonovine, have complex pharmacological properties with potential actions at dopaminergic and serotonergic as well as α-adrenergic receptors (Müller-Schweinitzer and Weidmann, 1978), and arteries from different vascular beds are pharmacologically heterogeneous (Bevan, 1979), it is important to clarify the nature of the contractile response to ergonovine of arteries from different vascular beds. In recent studies, we have demonstrated that atherosclerotic aortas from rabbits fed a high-cholesterol diet are supersensitive to the constrictor effects of ergonovine (Henry and Yokoyama, 1980). In the present study, isolated rabbit coronary, carotid, and femoral arteries, and aortas were studied to characterize their response to ergonovine, to elucidate the responsible underlying mechanism, and to determine the impact of endogenous hyperlipidemia on contractile properties of isolated vessels from different beds.

Methods

Watanabe hereditary hyperlipidemic rabbits (WHHL rabbits) of either sex, aged 8-12 months (average = 10.2 months), were used. These animals exhibit consistent hereditary hyperlipidemia as a result of inbreeding (Watanabe, 1980; Watanabe et al., 1981). Controls were age-matched normal Japanese white rabbits. After blood samples were collected, the rabbits were anesthetized with pentobarbital sodium (30 mg/kg, iv). Coronary, carotid, and femoral arteries, and the descending thoracic aorta were isolated, cleaned of surrounding tissue, and cut into
helical strips approximately 1–3 mm wide and 12–15 mm long. For recording isometric force, strips were suspended in 30-ml muscle chambers containing buffer of the following composition (mM): NaCl, 118; KCl, 4.0; CaCl₂, 1.5; MgSO₄, 1.2; NaH₂PO₄, 1.2; NaHCO₃, 25; and glucose, 5 (Yokoyama and Henry, 1979), and equilibrated at 37°C with a 95% O₂–5% CO₂ gas mixture. Final pH was approximately 7.38. Isometric force was normalized for cross-sectional area of each strip by dividing the wet weight of the strip determined at the conclusion of the experiment by length, and was expressed as mg/cross-sectional area (mg/CSA) (Su et al., 1977; Henry and Yokoyama, 1980). An initial preload of 1.5 g for aorta, 1.0 g for femoral and carotid arteries, and 0.5 g for coronary artery was applied. At the end of the equilibration period, preload was adjusted to exactly 1.0 g for aorta, 0.6 g for carotid and femoral arteries, and 0.3 g for coronary artery. The total equilibration time before addition of drugs was 2 hours. A test contraction was induced by raising the KCl concentration to 24 mM. When developed tension attained its peak value, the strips were relaxed by rinsing with buffer without augmented potassium.

Concentration-response relations for ergonovine, serotonin, and phenylephrine were determined by the cumulative addition of each drug to the bath fluid. Pilot experiments showed that contractions of atherosclerotic aortas in response to higher concentrations of ergonovine were not fully relaxed by washing with buffer. Therefore, concentration-response experiments with ergonovine were not repeated in the same aortic preparation. To compare the effects of two agonists, concentration-response relations for each agonist were determined sequentially with the same strip after a rest interval of 1.5 hours. Results were independent of the order of testing and were, therefore, combined for analysis.

To compare the effects of antagonists, two different methods were used. In one procedure, two paired strips were employed in the experiments to study the potency and selectivity of antagonists. In a cumulative concentration schedule, a single agonist was administered to each strip. The agonist then was washed from the baths. In one arterial strip, a selected concentration of an antagonist was added, and after 60-minute contact with the antagonist, the concentration-response relation for the agonist was redetermined. In the other arterial preparation, which served as a control, the concentration-response relations for the agonist were repeated at corresponding time, but in the absence of an antagonist. There were no changes in the responsiveness of the control strip from different beds to the repeated exposures to the agonist, except that of the coronary strip to phenylephrine. In the coronary strip, the responsiveness to phenylephrine in the presence of a selected concentration of an antagonist was corrected for any spontaneous reductions in reactivity, as judged from the control strip. In the other procedure, arterial tone was raised with an agonist, and the strip was relaxed with a selected concentration of an antagonist. Arterial tone was allowed to equilibrate fully after addition of the antagonist. Force developed in response to ergonovine and phenylephrine was stable and sustained during the first 2 hours after addition of the drug. The decline in force developed in response to 1 μM ergonovine and 1 μM phenylephrine was less than 3% in aortic strips and 7 ± 2% in carotid, femoral, and coronary strips during the first hour after addition of the drugs, and during the subsequent 1 hour it was minimally depressed.

At the end of each experiment, the artery was minced and homogenized in a glass homogenizer in the same buffer as that used for force recording. Protein in the whole homogenate was estimated by the Lowry method with serum bovine albumin as standard (Lowry et al., 1951). Total cholesterol in the same tissue samples and in serum samples was assayed enzymatically as described previously (Henry and Yokoyama, 1980).

The threshold concentrations, one-half maximally effective dose (ED₅₀) values and maximum responses were determined from the log concentration-response curves for each agonist. The data with antagonists were analyzed according to the procedure of Arunlakshana and Schild (1959). The slope of the regression and the pA₂ value (the negative logarithm of that concentration of the antagonist which requires twice as high a concentration of the agonist to elicit a given response) were estimated from a Schild plot.

Results were expressed as mean ± SEM. The significance of the difference between group means was assessed with the t-test for unpaired samples. Differences between sequential mean values in the same group were assessed with the t-test for paired samples. The following pharmacological agents were used: ergonovine maleate (Sandoz Pharmaceuticals); serotonin creatinine sulfate (Sigma); 1-phenylephrine hydrochloride (Sigma); prazosin hydrochloride (Pfizer Co. Ltd); cyproheptadine hydrochloride (Mark, Sharp & Dohme); methysergide bimaleate (Sandoz Pharmaceuticals). The drugs were dissolved in distilled water and diluted in buffer. All concentrations were expressed as final concentrations.

### Results

#### Assay of Plasma and Tissue Cholesterol and Triglyceride

The average values for total cholesterol in serum from control (n = 22) and WHHL rabbits (n = 23) were 45 ± 6 and 468 ± 90 mg/dl, and corresponding values for triglyceride were 43 ± 20 and 330 ± 93 mg/dl. These values are in agreement with those reported by Watanabe (1980). The rise in cholesterol is largely reflective of increased concentrations of low density lipoproteins (Tanzawa et al., 1980).

#### TABLE 1

| Arterial Tissue Cholesterol Concentrations in Normal and WHHL Rabbits |
|---------------------------------|---------|-----------|
|                                | No.     | mg/g wt   |
|                                |         | mg/g protein |
| Aorta                           |         |           |
| C                               | 9       | 9.5 ± 2.5 |
| W                               | 9       | 21.5 ± 1.0 |
| Coronary                        |         |           |
| C                               | 5       | 4.7 ± 0.6 |
| W                               | 7       | 7.3 ± 0.5 |
| Carotid                         |         |           |
| C                               | 8       | 4.5 ± 0.3 |
| W                               | 8       | 6.6 ± 0.7 |
| Femoral                         |         |           |
| C                               | 8       | 5.0 ± 1.1 |
| W                               | 8       | 6.6 ± 1.1 |

All results were expressed as mean ± SEM. P values were calculated on the basis of t-test for unpaired samples. C = control rabbits, W = WHHL rabbits.

* P < 0.05; †P < 0.01; ‡P < 0.001.
The total cholesterol content in aortas and coronary arteries from WHHL rabbits was significantly increased, compared with values in control animals (Table 1). Carotid and femoral arteries from diseased animals had increased total cholesterol content 1.4 times greater than that in vessels from the control rabbits. The differences in these values between the two groups were not statistically significant.

Macroscopic study of vessels from WHHL rabbits indicated that all the segments of the descending thoracic aorta used in the force measurement had grossly visible dots of lipid deposition, but there were no macroscopic atherosclerotic lesions in coronary, carotid, and femoral arteries examined.

Responses of Coronary Strips

The concentration-response relations for ergonovine of coronary arteries from control and WHHL rabbits are shown in Figure 1. The curve for the WHHL group was shifted to the left. The threshold concentrations, one-half maximally effective dose (ED₅₀) values, and maximum responses derived from the concentration-response experiments are shown in Table 2. The threshold concentration and the ED₅₀ from the WHHL group were significantly lower than those in the control group. However, the maximum response for the WHHL vessels was not significantly increased. Thus, the results do not simply reflect a nonspecific increase in contractile response. The curves for serotonin (Fig. 2) and phenylephrine in the two groups of coronary arteries were similar. The threshold concentration and the ED₅₀ were not different in the two groups (Table 2). The supersensitivity of coronary arteries from WHHL rabbits to ergonovine was not accompanied by an increase in the sensitivity to serotonin and phenylephrine.

Responses of Aortic Strips

Figure 3 depicts the log concentration-response relations for ergonovine of aortas from control and WHHL rabbits. The concentration-response curve of vessels from hyperlipidemic rabbits demonstrated an atypical sigmoid configuration and differed markedly from that of controls. The threshold concentration in aortic strips from the WHHL group was 1000 times lower than that in control group vessels. In addition, the ED₅₀ was reduced significantly, and the maximum response was significantly augmented in vessels from WHHL group (Table 2). These results are in agreement with our previous observation that isolated atherosclerotic aortas from rabbits fed a high cholesterol diet are supersensitive to the constrictor effects of ergonovine (Henry and Yokoyama, 1980).

The concentration-response curve for serotonin in the two groups of aortic strips are shown in Figure 4. The curve of vessels from the WHHL group was shifted to the left and exhibited significantly reduced values for the threshold concentration and the ED₅₀ (Table 2). The maximum response for the WHHL vessels was also significantly increased.

The concentration-response relations for phenylephrine were similar in the two groups of arteries. The threshold concentration, ED₅₀, and maximum response were not different in the two groups (Table 2).

Responses of Carotid and Femoral Strips

The concentration-response relations for ergonovine in carotid and femoral arteries were similar for control and WHHL rabbits. The threshold concentration, ED₅₀, and maximum response were not different in the two groups (Table 2). Accordingly, the reactivity of carotid and femoral arteries from WHHL rabbits to the vasoconstrictor effects of ergonovine was not altered, in contrast to the response of coronary artery and aorta. The concentration-response relations for serotonin and phenylephrine in the carotid and femoral arteries demonstrate that vascular reactivities to these agonists were similar with respect to threshold
TABLE 2
Threshold Concentrations, ED50 Values, and Maximum Responses in Arterial Strips from Normal and WHHL Rabbits

<table>
<thead>
<tr>
<th></th>
<th>Ergonovine</th>
<th>Serotonin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Threshold</td>
<td>ED50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>(3.7 ± 0.9) x 10^-7 M</td>
<td>(2.7 ± 0.4) x 10^-8 M</td>
</tr>
<tr>
<td>W</td>
<td>(3.6 ± 1.0) x 10^-10 M</td>
<td>(8.4 ± 1.6) x 10^-7 M</td>
</tr>
<tr>
<td>Coronary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>(7.2 ± 0.6) x 10^-10 M</td>
<td>(3.0 ± 1.1) x 10^-4 M</td>
</tr>
<tr>
<td>W</td>
<td>(5.9 ± 1.4) x 10^-11 M</td>
<td>(9.3 ± 2.4) x 10^-4 M</td>
</tr>
<tr>
<td>Carotid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>(2.8 ± 0.9) x 10^-9 M</td>
<td>(5.6 ± 1.1) x 10^-7 M</td>
</tr>
<tr>
<td>W</td>
<td>(4.1 ± 0.9) x 10^-9 M</td>
<td>(7.2 ± 0.3) x 10^-7 M</td>
</tr>
<tr>
<td>Femoral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>(6.7 ± 1.1) x 10^-10 M</td>
<td>(3.5 ± 0.8) x 10^-7 M</td>
</tr>
<tr>
<td>W</td>
<td>(2.8 ± 1.1) x 10^-10 M</td>
<td>(4.5 ± 0.8) x 10^-7 M</td>
</tr>
</tbody>
</table>

concentration, ED50, and maximum response (Table 2).

Effects of Antagonists
To clarify the mechanisms responsible for ergonovine-induced contraction, experiments with selected antagonists were performed. Prazosin was chosen as a blocking agent of the postjunctional α-adrenergic receptor, since it had repeatedly been shown to have negligible serotonin antagonistic activity (Doxey et al., 1977; Cohen et al., 1979). Cyproheptadine was used as a blocking agent of the serotonin receptor (Apperley et al., 1976, 1980).
Prazosin and cyproheptadine in concentrations ranging between 0.01 and 1 μM had no effect on resting arterial tone, as observed previously (Henry and Yokoyama, 1980). The results obtained with the antagonistic activity of cyproheptadine against serotonin and phenylephrine showed that this agent was a selective and competitive antagonist of serotonin in carotid and femoral arteries and aorta (Table 3). Thus, cyproheptadine (0.1 μM) was used to provide serotonergic blockade in these arteries. This concentration of the drug produced a marked reduction in the magnitude of the contractile response to serotonin of coronary artery (Fig. 5B), and it also suppressed the response to phenylephrine and 20 mM KCl by 92% (n = 4) and 96% (n = 4). The depression of cyproheptadine lacks selectivity for serotonergic receptors in coronary arteries and may reflect an effect of Ca ++ antagonism or nonspecific depression. Accordingly, an additional serotonergic antagonist, methysergide, was examined in coronary arterial preparations. The antagonistic activity of a selected concentration (0.3 μM) of methysergide showed that the concentration-response curve for serotonin was displaced to the right, with a reduction in maximum tension developed (Fig. 5C), and that the curve for phenylephrine was not affected (n = 5). This antagonist did not depress the contractile response to 20 mM KCl (n = 4), which suggested that it possessed little nonspecific blocking activity. These findings indicate that methysergide is a selective and noncompetitive antagonist against serotonergic receptors in coronary artery. Moreover, this ergot derivative raised the resting tone in the concentration higher than 0.03 μM in accord with recent reports suggesting some agonist activity on coronary artery (Muller-Schweinitzer, 1980; Sakasashi and Yonemura, 1980). The agonist activity of the drug (0.3 μM) was 14 ± 4% of constrictor responses to equimolar concentration of serotonin (n = 5).

**TABLE 3** Interaction between Two Agonists and Cyproheptadine in Various Rabbit Isolated Vessels

<table>
<thead>
<tr>
<th>Serotonin</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PA2</strong></td>
<td><strong>Slope</strong></td>
</tr>
<tr>
<td>Aorta</td>
<td>9.01</td>
</tr>
<tr>
<td>Carotid</td>
<td>9.01</td>
</tr>
<tr>
<td>Femoral</td>
<td>8.70</td>
</tr>
</tbody>
</table>

Each value is the mean of 8 to 10 estimates.
FIGURE 5. Effect of cyproheptadine (0.1 μM) and methysergide (0.3 μM) on the concentration-response relations for serotonin in control coronary strips. The abscissa is concentration of an agonist (−log M) and the ordinate is the contraction expressed as percentage of maximum contraction. Panel A: concentration-response curves without the antagonist. Panel B: concentration-response curve in the presence of cyproheptadine. Panel C: concentration-response curve in the presence of methysergide. Each curve is the average values of responses from four or five preparations in each case. Vertical bars indicate SEM.

The inhibitory effects of prazosin and cyproheptadine on arterial contractions in response to ergonovine are summarized in Figure 6. In control rabbits, 0.1 μM prazosin reduced arterial tone in aortic, carotid, and femoral arteries in response to 1 μM ergonovine by 94, 95, and 95%. In contrast, coronary contraction elicited by 1 μM ergonovine was suppressed only minimally by 0.1 and 1 μM prazosin. On the other hand, contractions of coronary artery in response to 1 μM ergonovine were completely abolished by 0.1 μM cyproheptadine. Of note, this agent did not suppress the response to ergonovine in any other types of artery examined in this study. Serotonergic blockade with 0.3 μM methysergide of coronary arteries shifted the concentration-response curve for ergonovine to the right and reduced the maximum tension developed (Fig. 7B). The results of the experiments with antagonists indicate that ergonovine-induced contractions were mediated by an α-adrenergic mechanism in aortic, carotid, and femoral arterial preparations, but by a serotonergic mechanism in coronary arterial preparations.

In WHHL rabbits, 0.1 μM prazosin exerted similar inhibitory effects on carotid and femoral arteries in response to 1 μM ergonovine. However, 0.1 μM cyproheptadine did not inhibit the response in these preparations. Coronary arteries stimulated with 1 μM ergonovine were insensitive to 0.1 and 1 μM prazosin. With 0.1 μM cyproheptadine, coronary
FIGURE 7. Effects of methysergide (0.3 μM) on the concentration-response relations for ergonovine in coronary strips from control (B) and WHHL rabbits (C). The abscissa is concentration of an agonist (-logM) and the ordinate is the contraction expressed as percentage of maximum contraction. Panel A: concentration-response curves without methysergide. Panels B and C: concentration-response curves in the presence of methysergide. Each curve is the average values of responses from six and four preparations in each group. Vertical bars indicate SEM.

contraction evoked by 1 μM ergonovine were completely abolished. With 0.3 μM methysergide, the concentration-response relations for ergonovine were shifted to the right, and the maximum tension developed was reduced in this artery (Fig. 7C). The blocking effect of 0.1 and 1 μM prazosin was significantly reduced in aortic preparations compared to responses seen in the control group. In aortas stimulated with 1 μM ergonovine, relaxations induced by 0.1 μM cyproheptadine were significantly greater in vessels from hyperlipidemic rabbits than those from control rabbits. Moreover, contractions evoked in aortas from WHHL rabbits by 0.001 μM ergonovine were inhibited considerably by 0.1 μM cyproheptadine (75 ± 4%, n = 4), but only minimally by 0.1 and 1 μM prazosin (6 ± 2%, n = 4). Results of these experiments indicate that coronary arteries, as well as aortas from WHHL rabbits, are supersensitive to the constrictor effects of ergonovine, and that altered responses to this drug are mediated predominantly by a serotonergic mechanism.

Discussion

The WHHL rabbit is a strain with consistently inherited hyperlipidemia produced by inbreeding since 1973 (Watanabe, 1980). The animals exhibit abnormally elevated concentrations of serum cholesterol and triglyceride. Gross and microscopic evidence of aortic atherosclerosis appears in every animal at 5 months of age. However, coronary atherosclerosis appears later. Coronary arteries used in our study were devoid of atherosclerotic lesions detectable macroscopically, but had increased cholesterol content 2-fold greater than that in vessels from control rabbits.

The results obtained in this study demonstrate that vasoconstrictor effects of ergonovine on selected arteries of different types from control rabbits are mediated by different mechanisms. Coronary effects are mediated mainly through activation of serotonergic receptors and aortic, carotid, and femoral effects through α-adrenergic receptors. Furthermore, coronary arteries from hyperlipidemic rabbits are supersensitive to the constrictor effects of ergonovine, even though they are free from demonstrable macroscopic atherosclerotic lesions. The results confirm our previous observation (Henry and Yokoyama, 1980) that aortas with gross macroscopic atherosclerosis are markedly supersensitive to ergonovine and serotonin. The supersensitivity in both types of vessels was mediated by an altered serotonergic responsiveness.

Ergot alkaloids, such as ergotamine and ergonovine, have complex pharmacological properties. They may act as either antagonists or partial agonists for dopaminergic or serotonergic as well as α-adrenergic receptors. Previous observations by Innes (1962) and Müller-Schweinitzer and Stürmer (1974), indicating that ergonovine and ergotamine stimulate α-adrenergic receptors in isolated rabbit aortas and canine saphenous veins, are confirmed in this study and extended to carotid and femoral arteries of rabbits. Recent data suggest that ergonovine induces contraction of canine coronary arteries by stimulating serotonergic receptors (Müller-Schweinitzer, 1980; Sakanashi and Yonemura, 1980). The mechanism of ergonovine-induced contractions of rabbit arteries was defined by the use of specific antagonists. Prazosin was chosen as the competitive α-adrenergic.
antagonist, since it had negligible serotonergic receptor antagonist activity (Doxey et al., 1977; Cohen et al., 1979). The antagonist activity of cyproheptadine, a drug classified as a serotonergic antagonist (Apperley et al., 1976, 1980), was examined in the four different types of arteries. In the femoral and carotid arteries and aorta, cyproheptadine was a selective and competitive antagonist against serotonergic receptors, and its effect on adrenergic receptors was negligible. These data correspond to the findings obtained on rat aorta and dog femoral artery (Apperley et al., 1976, 1980). In these arterial preparations, vasoconstrictor response to ergonovine was not suppressed by cyproheptadine, but completely abolished by prazosin, indicating that it is mediated through activation of \( \alpha \)-adrenergic receptors. In contrast, the present results show that cyproheptadine effectively suppresses coronary contractions induced by serotonin and ergonovine, and that this drug also has nonspecific inhibitory effects on coronary arteries. Thus, the selectivity of another serotonergic antagonist, methysergide, was examined in coronary arterial preparations. This agent was a selective serotonergic antagonist in this artery and had also an antagonistic action on the contractile response to ergonovine which was not inhibited by prazosin. These results indicate that coronary contractions elicited by ergonovine are mediated through a serotonergic mechanism. These observations imply that different large-sized rabbit arteries contract in response to ergonovine due to stimulation of different receptors present in vascular smooth muscles.

The concentration-response relations of coronary arteries from WHHL rabbits showed a leftward shift for ergonovine, but not for serotonin and phenylephrine. Therefore, hyperlipidemia in vivo appears to sensitize coronary arteries to ergonovine. Two serotonergic antagonists, methysergide and cyproheptadine, largely suppressed the constrictor effect of ergonovine in coronary arteries from both groups, which suggests that the supersensitivity was mediated by altered serotonergic responsiveness. The reason why the constrictor response to serotonin of coronary arteries from WHHL group is not altered is unknown. This lack of supersensitivity may reflect heterogeneous alterations in stimulus-response relationships of the tissue exposed to endogenous hyperlipidemia, or differences in affinity or efficacy of agonists. It also remains possible that ergonovine may operate through its own specific receptors, which are similar to, but not the same as, serotonergic receptors.

This study confirmed our previous observations that, in control aortas, ergonovine stimulated \( \alpha \)-adrenergic receptors, and that atherosclerotic aortas were supersensitive to ergonovine, mainly through a serotonergic mechanism (Henry and Yokoyama, 1980). The supersensitivity of coronary artery and aorta from WHHL rabbits was not accompanied by alterations in constrictor responses to KCl or phenylephrine. These findings strongly suggest that the altered responsiveness of atherosclerotic arteries did not result exclusively from nonspecific structural changes such as smooth muscle hyperplasia or fibrosis.

We had previously shown that the altered reactivity of atherosclerotic arteries to ergonovine was not caused by a deficient synthesis of prostacyclin (Henry and Yokoyama, 1980).

The hypothesis that incorporation of cholesterol into the membrane of the arterial smooth muscle cells which occurs in the early stages of atherosclerosis (Small and Shipley, 1974) may operate through its own specific receptors, and that atherosclerotic alterations in stimulus-response relations of the tissue exposed to endogenous hyperlipidemia may acquire altered contractile responses to specific vasoconstrictor stimuli, a phenomenon that could play a role in the pathophysiology of angina-associated spasm.

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