H₁ and H₂ receptors mediate postexercise hyperemia in sedentary and endurance exercise-trained men and women

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McCord, Jennifer L., and John R. Halliwill. H₁ and H₂ receptors mediate postexercise hyperemia in sedentary and endurance exercise-trained men and women. J Appl Physiol 101: 1693–1701, 2006.—In sedentary individuals, H₁ receptors mediate the early portion of postexercise skeletal muscle hyperemia, whereas H₂ receptors mediate the later portion. It is not known whether postexercise hyperemia also presents in endurance-trained individuals. We hypothesized that the postexercise skeletal muscle hyperemia would also exist in endurance-trained individuals and that combined blockade of H₁ and H₂ receptors would abolish the long-lasting postexercise hyperemia in trained and sedentary individuals. We studied 28 sedentary and endurance trained men and women before and through 90 min after a 60-min bout of cycling at 60% peak O₂ uptake on control day and combined H₁- and H₂-receptor antagonist days (fexofenadine and ranitidine). We measured arterial pressure (brachial auscultation) and femoral blood flow (Doppler ultrasound). On the control day, femoral vascular conductance (calculated as flow/pressure) was elevated in all groups 60 min after exercise (sedentary men: Δ86 ± 35%, trained men, Δ65 ± 18%; sedentary women, Δ61 ± 19%, trained women: Δ59 ± 23%, where A is change; all P < 0.05 vs. preexercise). In contrast, on the histamine antagonist day, femoral vascular conductance was not elevated in any of the groups after exercise (sedentary men: Δ21 ± 17%, trained men: Δ9 ± 5%, sedimentary women: Δ19 ± 4%, trained women: Δ11 ± 11%; all P > 0.16 vs. preexercise; all P < 0.05 vs. control day). These data suggest postexercise skeletal muscle hyperemia exists in endurance trained men and women. Furthermore, histaminergic mechanisms produce the long-lasting hyperemia in sedentary and endurance-trained individuals.

skeletal muscle; regional blood flow; histamine; athletes; hypotension

POSTEXERCISE HYPOTENSION OCCURS after a single bout of dynamic exercise (13, 24, 30). In most subjects, postexercise hypotension results from a persistent rise in peripheral vascular conductance that is not completely offset by postexercise increases in cardiac output (13, 16, 17), although endurance exercise-trained men are an exception (40). In sedentary and normally active men and women, the rise in peripheral vascular conductance leading to postexercise hypotension is mediated by individual contributions of histamine 1 (H₁) and histamine 2 (H₂) receptors in the vasculature, although the primary contribution of each receptor occurs at different times. Our laboratory found that with ingestion of a H₁-receptor antagonist, the postexercise vasodilation is markedly reduced and the fall in blood pressure is blunted 30 min after exercise, but this attenuation becomes minimal at 60 and 90 min after exercise (29). Then H₂ receptors were found to exhibit their peak effect on the postexercise hypotension response at 60 and 90 min after exercise, whereas at 30 min there was minimal contribution (31). What is still unknown is whether a combined blockade of H₁ and H₂ receptors can abolish the 90-min period of postexercise hyperemia and consequent postexercise hypotension.

A bout of aerobic exercise also produces postexercise hypotension in the endurance trained population (40). However, endurance-trained men do not exhibit the postexercise augmentation of systemic vascular conductance (and cardiac output is decreased postexercise), and the mechanisms of postexercise hypotension remain unknown in this population (40). Because of the fact that systemic vascular conductance is unchanged postexercise, it would be easy to surmise that skeletal muscle hyperemia is absent in this population. However, it could also be surmised that vasodilation and hyperemia in skeletal muscle are masked by a reduction in vascular conductance elsewhere (perhaps as compensation for the decrease in stroke volume and cardiac output), such that systemic conductance appears unchanged. It may be more likely that skeletal muscle is vasodilated during recovery from exercise in trained individuals but that this is masked by constriction elsewhere than that this mechanism is absent in trained individuals. Thus, at present, it is not known whether the endurance-trained population exhibit postexercise hyperemia in the skeletal muscle vasculature and, if it is present, whether H₁ and H₂ receptors mediate this response, but both concepts seem plausible based on prior observations in sedentary and normally active men and women.

Therefore, three questions were asked in this study: 1) is there a regional increase in skeletal muscle blood flow postexercise in endurance exercise-trained men and women? 2) if so, are histamine receptors responsible for this postexercise hyperemia in this population? and 3) can a combined blockade of H₁ and H₂ receptors abolish the entire postexercise hyperemia in both endurance-trained and sedentary populations? We hypothesized that the endurance exercise-trained men and women would both exhibit a postexercise skeletal muscle hyperemia and that blockade of histamine receptors would abolish this response. Furthermore, we hypothesized that in all subject populations, a combined blockade of H₁ and H₂ receptors would abolish the entire postexercise hyperemia response (~30–90 min).

METHODS

This study was approved by the Institutional Review Board of the University of Oregon, and each subject gave informed, written consent before participation.

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Subjects

Twenty-eight healthy, nonsmoking, normotensive subjects between the ages of 19 and 34 yr participated in this study. The subjects were classified and separated into four groups: endurance exercise-trained men and women (7 men and 7 women; >4 h of endurance exercise per week) and sedentary men and women (7 men and 7 women; ≤30 min of exercise per week). Subjects were taking no medication other than oral contraceptives. Women subjects had a negative pregnancy test on the screening visit.

Screening Visit

Subjects reported to the laboratory for a screening visit and cycle ergometer test at least 2 h postprandial and abstained from caffeine and alcohol for 12 h before and exercise for 24 h before the screening visit. Subjects performed an incremental cycle exercise test (Lode Excaliber, Groningen, The Netherlands) comprised of 1-min workload increments to determine peak O2 uptake (\(\dot{V}_{O_2}\)peak). Specifically, after a 2-min warm-up period of easy cycling (20–30 W), workload increased by 20, 25, or 30 W every minute. Selection of the workload increment was subjective, with the goal of producing exhaustion within 8–12 min. Whole body O2 uptake was measured via a mixing chamber (Parvomedics, Sandy, UT) integrated with a mass spectrometer system (Marquette MGA 1100, MA Tech Services, St. Louis, MO). All subjects reached subjective exhaustion (rating of perceived exertion on the Borg (4) scale of 19–20) within the 8- to 12-min period. After the subjects rested for 15–20 min, they returned to the cycle ergometer for assessment of the workload corresponding to a steady-state O2 consumption of 60% of \(\dot{V}_{O_2}\)peak. This workload was used on the 2 study days for the 60-min exercise bout. Subjects self-reported activity levels on two questionnaires (2, 25).

Study Visits

Subjects reported for parallel experiments on 2 separate days. The order of experiments was randomized between a combined H1- and H2-receptor antagonist (fexofenadine and ranitidine) and a control day. For both study days, subjects reported for the study at least 2 h before exercise, during the last minute of exercise, and postexercise at 30, 60, and 90 min. Samples were collected in prechilled tubes and immediately separated (plasma) and stored (plasma and whole blood) at −80°C until analysis. The concentration of histamine was then assessed by measuring plasma and whole blood concentrations with a commercially available enzyme immunoassay kit and are expressed in nanograms per milliliter (IBL-America, Minneapolis, MN) (8). The reported lower limit for detection of histamine is 0.3 ng/ml. Across the range of values in this study, interassay and intra-assay coefficients of variation are 11.5 and 7.8%, respectively.

Experimental Protocol

On study days, subjects were given water with or without fexofenadine and ranitidine 60 min before the start of exercise. The subjects were then laid in the supine position for instrumentation. A venous catheter was inserted into the right arm in the antecubital region to obtain blood samples. Exercise consisted of a 60-min period of seated upright cycling at 60% \(\dot{V}_{O_2}\)peak. Exercise of this intensity and duration produces a sustained (≈2 h) postexercise hypotension (13). During exercise, subjects received 15 ml of water per kilogram of body weight to replace water loss due to sweating. Measurements were taken for 30 min before and through 90 min after a 60-min bout of exercise. Baseline (preexercise), 30-min, 60-min, and 90-min postexercise measurements included cardiac output, heart rate, arterial pressure, femoral blood flow, brachial blood flow, skin blood flow, and a blood sample. During exercise, blood pressure, and heart rate were measured every 10 min. At the end of the protocol, maximum skin blood flow values were obtained through local heating to 43°C. All pre- and postexercise measurements were made in the supine position.

Measurements

Heart rate and arterial pressure. Heart rate and arterial pressure were monitored throughout all experimental procedures. Heart rate was monitored using a five-lead electrocardiogram (model Q710, Quinton Instruments, Bothell, WA). Arterial pressure was measured in the arm by using an automated auscultometric device (Dinamap Pro100 vital signs monitor, Critikon, Tampa, FL).

Cardiac output. Cardiac output was estimated using an open-circuit acetylene washin method as described previously (22, 28). This method allows for the noninvasive estimation of cardiac output. We chose an open-circuit method because subjects are exposed to stable oxygen and carbon dioxide levels throughout the measurement in contrast to rebreath techniques. Subjects breathed a gas mixture containing 0.6% acetylene-9.0% helium-20.9% oxygen-balance nitrogen for 8–10 breaths via a two-way non-rebreathing valve. During the washin phase, breath-by-breath acetylene and helium uptake were measured by a respiratory mass spectrometer (Marquette MGA 1100), and tidal volume was measured via a pneumotach (model 3700, Hans Rudolph, Kansas City, MO) linearized by the technique of Yeh et al. (42) and calibrated by using test gas before each study. The pneumotach and valve system had a combined dead space of 24 ml. Cardiac output calculations have been described previously (22). Stroke volume was determined from cardiac output/heart rate. Systemic vascular conductance was calculated as cardiac output/mean arterial pressure (expressed as ml·min⁻¹·mmHg⁻¹).

Leg and arm blood flow. Femoral and brachial artery diameters and velocities were measured using an ultrasound probe (10-MHz linear-array vascular probe, GE Vingmed System 5, Horton, Norway). The entire widths of the arteries were imasoned with an angle of 60°. Velocity measurements were taken immediately before diameter measurements. Leg and arm blood flows were each calculated as artery cross-sectional area multiplied by femoral or brachial mean blood velocity, and this value was doubled to represent both legs or arms.

H1 receptors were blocked with 540 mg fexofenadine. This amount of oral fexofenadine has been shown to adequately block H1 receptors (time to peak concentration <1.5 h and half-life <12 h) (37). H2 receptors were blocked with 300 mg ranitidine. This amount of oral ranitidine has been shown to adequately block H2-receptors with a peak plasma concentration at 2.2- and a 2.6-h half life. Responses are >90% inhibited within 1 h and remain inhibited 6 h after administration (6, 12). Fexofenadine and ranitidine do not appear to cross into the central nervous system or possess sedative actions (6). Furthermore, these drugs do not have any direct cardiovascular effects in the absence of histamine-receptor stimulation (i.e., when given under normal resting conditions, these drugs do not elicit any changes in heart rate, blood pressure, or smooth muscle tone) (6, 29, 31). Blockade of H1 receptors prevents the formation of local vasodilator substances such as nitric oxide and prostaglandins in response to histamine administration, whereas blockade of H2 receptors prevents the decrease in smooth muscle intracellular calcium levels that usually occurs with binding of histamine (6, 19). Blockade of either H1 or H2 receptors does not alter histamine release and should not affect histamine concentrations. To assess histamine concentrations during the study, blood samples were taken via an intravenous catheter before exercise, during the last minute of exercise, and postexercise at 30, 60, and 90 min. Samples were collected in prechilled tubes and immediately separated (plasma) and stored (plasma and whole blood) at −80°C until analysis. The concentration of histamine was then assessed by measuring plasma and whole blood concentrations with a commercially available enzyme immunoassay kit and are expressed in nanograms per milliliter (IBL-America, Minneapolis, MN) (8). The reported lower limit for detection of histamine is 0.3 ng/ml. Across the range of values in this study, interassay and intra-assay coefficients of variation are 11.5 and 7.8%, respectively.
Differences were considered significant when within groups: drug vs. time; between groups: sex, trained status.

Data Analysis

V̇O₂ peak was calculated as flow for both legs/mean arterial pressure (expressed as ml·min⁻¹·mmHg⁻¹). Brachial vascular conductance was calculated as flow for both arms/mean arterial pressure (expressed as ml·min⁻¹·mmHg⁻¹).

Cutaneous vascular conductance. Red blood cell flux was used as an index of skin blood flow via laser-Doppler flowmetry (DRT4, Moor Instruments, Devon, UK). Laser-Doppler probes were placed one each on the forearm and thigh. Skin blood flows were expressed as cutaneous vascular conductance, calculated as laser-Doppler flux/mean arterial pressure, and they were normalized to the maximal values achieved during local heating to 43°C (23).

Plasma volume. Percent change in plasma and blood volume from preexercise were calculated from changes in hemoglobin and hematocrit by the method of Dill and Costill (7).

Preexercise Hemodynamics

Preexercise hemodynamics are shown in Table 2. Supine resting heart rate and mean arterial pressure were not different within subjects between control and H₁- and H₂-receptor antagonist days (P > 0.20). Endurance-trained women and men exhibited a lower resting heart rate than their sedentary counterparts (P < 0.05).

Exercise

The goal was to have subjects exercise for 60 min at 60% V̇O₂ peak. Average workloads are shown in Table 1 for each group. Heart rate reserve (heart rate reserve is defined as maximal heart rate achieved during V̇O₂ peak testing minus the resting supine heart rate), heart rate, and mean arterial pressure were not different within groups between control and H₁- and H₂-receptor antagonist days (P > 0.20; Table 3). However, endurance-trained women showed a lower heart rate reserve, heart rate, and mean arterial pressure than their male equivalents (P < 0.05).

Postexercise Hemodynamics

Mean arterial pressure was decreased after exercise in all subject groups on the control day (P < 0.05). The H₁- and H₂-receptor antagonists prevented the decrease in mean arterial

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sedentary Men</th>
<th>Trained Men</th>
<th>Sedentary Women</th>
<th>Trained Women</th>
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<tr>
<td>n</td>
<td>7</td>
<td>7</td>
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<td>7</td>
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<td>Age, yr</td>
<td>24.0±5.0</td>
<td>22.1±2.7</td>
<td>25.6±4.6</td>
<td>22.9±2.5</td>
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<tr>
<td>Height, cm</td>
<td>181.9±4.6†</td>
<td>180.9±4.1†</td>
<td>166.1±9.6</td>
<td>168.1±2.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.8±6.5</td>
<td>77.4±11.3†</td>
<td>67.2±18.7</td>
<td>59.0±4.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.0±1.5</td>
<td>23.7±3.2</td>
<td>24.3±6.5</td>
<td>20.9±1.6</td>
</tr>
<tr>
<td>V̇O₂ peak, ml·kg⁻¹·min⁻¹</td>
<td>38.4±3.5†</td>
<td>58.4±3.8†</td>
<td>27.5±5.6</td>
<td>42.9±5.7*</td>
</tr>
<tr>
<td>Workload at 60% of V̇O₂ peak, W</td>
<td>116.0±13.9†</td>
<td>196.6±23.9†</td>
<td>67.9±23.3</td>
<td>106.4±8.8*</td>
</tr>
<tr>
<td>Baecke sport index, arbitrary units</td>
<td>7.9±0.9</td>
<td>14.6±3.7*</td>
<td>9.1±0.9</td>
<td>14.2±3.6*</td>
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<tr>
<td>Index of physical activity, MET·h/wk</td>
<td>56.7±16.7</td>
<td>190.0±68.0*</td>
<td>78.7±22.1</td>
<td>177.2±58.7*</td>
</tr>
</tbody>
</table>

Values are means ± S.D. n, no. of subjects. V̇O₂ peak, O₂ consumption; MET, metabolic equivalents. *P < 0.05 vs. sedentary within same sex. †P < 0.05 vs. women within same training status.

Table 2. Preexercise hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Sedentary Men</th>
<th>Trained Men</th>
<th>Sedentary Women</th>
<th>Trained Women</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Blockade</td>
<td>Control</td>
<td>Blockade</td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
<td>84.0±4.3</td>
<td>80.3±3.3</td>
<td>81.0±1.9</td>
<td>79.8±1.9</td>
</tr>
<tr>
<td>Systemic vascular conductance, ml·min⁻¹·mmHg⁻¹</td>
<td>69.9±6.6</td>
<td>68.9±7.4</td>
<td>67.9±8.6</td>
<td>69.0±5.1†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>63.6±2.5</td>
<td>62.8±2.8</td>
<td>52.4±3.1†</td>
<td>50.7±2.6†</td>
</tr>
<tr>
<td>Stroke volume, ml/beat</td>
<td>93.1±9.4g</td>
<td>88.0±9.2</td>
<td>108.3±16.3‡</td>
<td>111.1±11.9‡</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.8±0.4</td>
<td>5.4±0.4</td>
<td>5.5±0.6‡</td>
<td>5.5±0.4</td>
</tr>
<tr>
<td>Femoral vascular conductance, ml·min⁻¹·mmHg⁻¹</td>
<td>4.2±0.5</td>
<td>4.6±0.7</td>
<td>4.7±1.1</td>
<td>4.3±1.2</td>
</tr>
<tr>
<td>Brachial vascular conductance, ml·min⁻¹·mmHg⁻¹</td>
<td>1.6±0.2</td>
<td>1.2±0.2</td>
<td>1.3±0.2*</td>
<td>1.2±0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 subjects for each group. *P < 0.05 vs. control at same time point. †P < 0.05 vs. sedentary within same sex. ‡P < 0.05 vs. women within same training status.

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pressure throughout recovery from exercise in all groups ($P < 0.05$; Fig. 1) compared with control day. Systemic vascular conductance was increased in endurance-trained women and sedentary men and women after exercise on the control day ($P < 0.05$; Fig. 1). The histamine antagonists blunted the rise in systemic vascular conductance after exercise in sedentary men and women ($P < 0.05$ vs. control). After exercise, there were no changes in systemic vascular conductance in trained men ($P > 0.33$), nor did the H$_1$- and H$_2$-receptor antagonists have an effect on systemic vascular conductance ($P > 0.55$ vs. control; Fig. 1).

Figure 2 shows heart rate, stroke volume, and cardiac output as percent changes from baseline to 30, 60, and 90 min after exercise. Heart rate was increased after exercise on both study days in endurance-trained men and sedentary men and women ($P < 0.05$). There were no differences between the 2 study days. Stroke volume was decreased after exercise in endurance-trained men ($P < 0.05$), whereas stroke volume was maintained in all other groups.

Femoral vascular conductance was increased after exercise in endurance-trained and sedentary men and women on the control day ($P < 0.05$). H$_1$- and H$_2$-receptor antagonists abolished these increases in all groups after exercise ($P < 0.05$ vs. control). Brachial vascular conductance increased after exercise in the endurance-trained men, whereas this increase was abolished with the H$_1$- and H$_2$-receptor antagonists ($P < 0.05$ vs. control). The other subject groups had no such changes in brachial vascular conductance ($P > 0.21$; Fig. 3).

**Cutaneous Vascular Conductance**

At 30 min after exercise, forearm and thigh cutaneous vascular conductances were not different from baseline values on the control day in endurance-trained women and sedentary men and women (Table 4; $P > 0.49$). However, endurance-trained men showed an increase in forearm and thigh cutaneous vascular conductances after exercise on the control day ($P < 0.05$). On the H$_1$- and H$_2$-receptor antagonist day, forearm and...
thigh cutaneous vascular conductances were unchanged from preexercise and compared with the control day in endurance-trained women and sedentary men and women (all $P < 0.28$). The exception again is the endurance-trained men, because they showed an increase in thigh cutaneous vascular conductance after exercise and showed an even greater increase on the $H_1$- and $H_2$-receptor antagonist day than the control day ($P < 0.05$).

**Plasma and Blood Volume**

Table 5 shows plasma and blood volumes for all groups in response to and recovery from exercise. All groups showed a decrease in plasma ($P < 0.05$) and blood ($P < 0.05$) volumes during exercise. There were no differences in plasma (all $P > 0.55$) or blood volume (all $P > 0.63$) changes during exercise between the 2 study days in the endurance trained men and sedentary men and women. On the control day, endurance exercise-trained men and women showed an increase in plasma and blood volumes during recovery from exercise (all $P < 0.05$), and this increase was not seen after exercise in the sedentary men and women (all $P > 0.29$). The $H_1$- and $H_2$-receptor antagonists prevented the increase in plasma and blood volume after exercise only in the endurance-trained women ($P < 0.05$) but not in the endurance-trained men ($P > 0.12$).

**Histamine Concentration**

The sedentary men and women showed no increases in histamine concentration in response to exercise in whole blood (preexercise: control $4.6 \pm 0.6$ ng/ml, antagonists $4.3 \pm 0.4$ ng/ml; exercise: control $4.9 \pm 0.5$ ng/ml, antagonists $3.8 \pm 0.5$ ng/ml; both $P > 0.38$ vs. preexercise) or plasma (preexercise: control $0.4 \pm 0.1$ ng/ml, antagonists $0.3 \pm 0.2$ ng/ml; exercise: control $0.2 \pm 0.1$ ng/ml, antagonists $0.3 \pm 0.2$ ng/ml; both $P > 0.24$ vs. preexercise). The endurance trained men and women showed no increases in histamine concentration in response to
exercise in whole blood (preexercise: control 2.9 ± 0.7 ng/ml, antagonists 3.4 ± 0.8 ng/ml; exercise: control 3.5 ± 0.9 ng/ml, antagonists 4.1 ± 0.9 ng/ml; both P > 0.32 vs. preexercise) or plasma (preexercise: control 0.3 ± 0.2 ng/ml; antagonists 0.3 ± 0.2 ng/ml; exercise: control 0.5 ± 0.2 ng/ml; antagonists 0.4 ± 0.2 ng/ml; both P > 0.26 vs. preexercise). Histamine concentrations did not differ from baseline or exercise values in whole blood or plasma during recovery from exercise (all P > 0.22). There were no differences between the 2 study days (all P > 0.37).

**DISCUSSION**

In sedentary to normally active individuals, H1-receptor-mediated vasodilation in large part mediates the early postexercise hypotension seen 30 min after a single bout of aerobic exercise (29). H2 receptors are responsible for the later stages of postexercise hypotension (~60–90 min) (31). The goal of this study was to determine whether postexercise hyperemia occurs in endurance exercise-trained men and women and, if so, whether this postexercise hyperemia mediated by H1 and H2 receptors. In agreement with our hypotheses, we found that postexercise hyperemia occurs in endurance exercise-trained men and women and that H1 and H2 receptors mediate the postexercise hyperemia. Another goal of this study was to determine whether a combined blockade of H1 and H2 receptors could completely abolish the 90-min period of postexercise hyperemia. We found that the entire 90-min period of postexercise hyperemia was abolished by the histamine-recept-

![Image](1698_H1_AND_H2_RECEPTORS_AND_POSTEXERCISE_HYPEREMIA.png)

**Table 4. Cutaneous vascular conductance**

<table>
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<th>Sedentary Men</th>
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<td>Forearm, %CVCmax</td>
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<tr>
<td>Preexercise</td>
<td>3.5 ± 1.0</td>
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<td></td>
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<td>5.8 ± 2.7</td>
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<td>5.0 ± 1.5</td>
<td></td>
<td>6.2 ± 2.8*</td>
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<tr>
<td>Postexercise 30 min</td>
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<td>5.0 ± 1.5</td>
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<td>6.2 ± 2.8</td>
<td>4.5 ± 1.3</td>
<td></td>
<td>2.6 ± 2.7</td>
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<tr>
<td>Postexercise 60 min</td>
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<td>2.9 ± 0.7</td>
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<tr>
<td>Postexercise 90 min</td>
<td>2.5 ± 1.4</td>
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<td>5.8 ± 2.3</td>
<td></td>
<td>2.6 ± 0.7</td>
<td>0.8 ± 0.7</td>
<td></td>
<td>3.0 ± 0.5</td>
<td>2.4 ± 0.6</td>
<td></td>
<td>2.1 ± 1.5</td>
<td>2.1 ± 0.3</td>
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<td>3.6 ± 0.3</td>
<td>5.1 ± 0.8</td>
<td></td>
<td>3.6 ± 0.3</td>
<td>5.1 ± 0.8</td>
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<tr>
<td>Thigh, %CVCmax</td>
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<tr>
<td>Preexercise</td>
<td>4.6 ± 1.4</td>
<td>9.1 ± 3.6</td>
<td></td>
<td>4.5 ± 0.5</td>
<td>5.7 ± 1.6</td>
<td></td>
<td>3.6 ± 1.3</td>
<td>3.6 ± 0.6</td>
<td></td>
<td>2.0 ± 0.3</td>
<td>3.4 ± 0.3</td>
<td></td>
<td>9.1 ± 2.2</td>
<td>8.8 ± 2.9</td>
<td></td>
<td>6.9 ± 1.6</td>
<td>13.1 ± 4.3†</td>
<td></td>
<td>4.1 ± 0.4</td>
<td>5.3 ± 0.9</td>
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<tr>
<td>Postexercise 30 min</td>
<td>9.1 ± 2.2</td>
<td>8.8 ± 2.9</td>
<td></td>
<td>6.9 ± 1.6</td>
<td>13.1 ± 4.3†</td>
<td></td>
<td>4.4 ± 0.7</td>
<td>2.5 ± 0.3</td>
<td></td>
<td>4.1 ± 0.4</td>
<td>5.3 ± 0.9</td>
<td></td>
<td>4.4 ± 0.7</td>
<td>2.5 ± 0.3</td>
<td></td>
<td>4.1 ± 0.4</td>
<td>5.3 ± 0.9</td>
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<td>5.3 ± 0.9</td>
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<tr>
<td>Postexercise 60 min</td>
<td>7.5 ± 2.6</td>
<td>8.2 ± 2.7</td>
<td></td>
<td>7.5 ± 1.8*</td>
<td>12.5 ± 3.4*</td>
<td></td>
<td>3.1 ± 1.8</td>
<td>1.5 ± 0.5</td>
<td></td>
<td>4.0 ± 0.6</td>
<td>5.7 ± 0.9</td>
<td></td>
<td>7.5 ± 2.6</td>
<td>8.2 ± 2.7</td>
<td></td>
<td>7.5 ± 1.8*</td>
<td>12.5 ± 3.4*</td>
<td></td>
<td>3.1 ± 1.8</td>
<td>1.5 ± 0.5</td>
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<tr>
<td>Postexercise 90 min</td>
<td>5.9 ± 1.7</td>
<td>6.4 ± 2.4</td>
<td></td>
<td>6.5 ± 1.0</td>
<td>8.6 ± 2.5</td>
<td></td>
<td>2.1 ± 1.5</td>
<td>2.1 ± 0.3</td>
<td></td>
<td>3.6 ± 0.3</td>
<td>5.1 ± 0.8</td>
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<td>5.9 ± 1.7</td>
<td>6.4 ± 2.4</td>
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<td>8.6 ± 2.5</td>
<td></td>
<td>2.1 ± 1.5</td>
<td>2.1 ± 0.3</td>
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Values are means ± SE; n = 7 subjects for each group. CVCmax, maximum cutaneous vascular conductance. *P < 0.05 vs. preexercise, †P < 0.05 vs. control at same time point.
showed that the postexercise hyperemia response could be -adrenergic-receptor blockade, suggesting the existence of a conductance after exercise was greater than that observed after presynaptic inhibition of norepinephrine release from sympathetic nerve activity, independent of changes in the level of sympathetic nerve activity, and thus the vasodilation that underlies postexercise hyperemia occurs in endurance exercise-trained men and women and is histaminergic in mechanism. Postexercise skeletal muscle hyperemia exhibits in endurance-trained men even though net peripheral vasodilation is absent (i.e., unchanged systemic vascular conductance postexercise). This suggests that vasoconstriction in other areas, perhaps the splanchnic or renal vascular beds, may offset the vasodilation in skeletal muscle in this population (34).

Our laboratory has shown in previous studies, with sedentary to normally active men and women, that individual contributions of H1- and H2-receptors mediate the postexercise hypotension response (29, 31). Therefore, it seemed plausible that with a combined blockade of H1 and H2 receptors, the postexercise hyperemia and hypotension responses would be eliminated. In agreement with this theory, the skeletal muscle hyperemia and hypotension were reduced if not abolished with combined histamine-receptor antagonists.
sympathetic withdrawal in response to the prevention of vasodilation in the leg. Thus overall systemic peripheral vasodilation is largely unchanged by histamine receptor blockade, but the contributing mechanisms to systemic vascular tone have been altered.

An interesting aspect of this study was the measurement of brachial vascular conductance in sedentary and endurance exercise-trained men and women. Endurance-trained men were the only group that had postexercise augmentation of brachial vascular conductance that was attenuated with the administration of histamine antagonists; however, there were inconsistent trends for a rise in brachial vascular conductance in the sedentary men as well. These findings contradict prior studies that found increased forearm or brachial vascular conductance after exercise (15, 31). Previously, our laboratory used the same Doppler ultrasound methodology to document the postexercise rise in brachial vascular conductance in normally active and sedentary men and women (31), so it does not appear that this divergent observation is related to methodology (e.g., plethysmography vs. ultrasonography). It may be that there is a training status-sex interaction that determines whether or not the inactive skeletal muscle vasodilates, because prior studies combined results from men and women and from sedentary and recreationally active individuals.

This leads us back to the question of why would the men, and particularly endurance-trained men, exhibit an inactive skeletal muscle histaminergic hyperemia during recovery from exercise? Could the endurance-trained male subjects have added upper body exercise to the 60 min of cycling? All subjects were allowed a bike position that was most comfortable to them during the hour of exercise. Perhaps the trained male subjects used their upper body to grip the handle bars and thus the inactive muscles (arms) were engaged in work. Or could the increase in brachial vascular conductance in trained men be due to a greater thermodynamic load and subsequent cutaneous vasodilation? The trained men had the highest workload for the 60 min of exercise; perhaps this intensity caused a greater thermodynamic load. Evidence for this to be true is an increase in forearm and thigh cutaneous vascular conductance from degranulated mast cells in most tissues or synthesized in non-mast-cell tissues such as neurons and cells in the walls of blood vessels by the actions of l-histidine decarboxylase (6, 18, 38). Nonetheless, histamine does appear to be the most likely candidate at this time based on completed studies.

**Perspectives.** Histamine antagonists might benefit those individuals who suffer from exercise-related syncope. Several types of endurance exercise (i.e., running, cycling, and swimming) have been shown to be the cause of symptoms of postexercise orthostatic intolerance (9, 20, 21). As well, certain populations, such as athletic subjects, have a high prevalence of syncope after exercise (36, 39). In some of these individuals, postexercise hypotension is exaggerated and leads to symptoms of orthostatic intolerance, including syncope (26). Because histamine receptors play a significant role in the “normal” postexercise hypotension response, histamine-receptor antagonists might be beneficial for those individuals who suffer from exercise-related vasovagal syncope.

In conclusion, ingestion of H1- and H2-receptor antagonists abolishes the vasodilation after exercise and blunts postexercise hypotension in endurance exercise-trained and sedentary men and women. These data advocate for histaminergic mechanisms responsible for the postexercise hyperemia in endurance exercise-trained men and women.

**ACKNOWLEDGMENTS**

We sincerely appreciate the time and effort put forth by the subjects who volunteered for this study. We also thank Julie Beasley for fantastic technical assistance. This study was conducted by J. L. McCord in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Oregon.

**GRANTS**

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