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

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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 workloads to determine peak VO2 uptake (VO2peak). 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 VO2 uptake was measured via a mixing chamber (Parvomedics, Sandy, UT) integrated with a mass spectrometry 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 8–12-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 VO2 consumption of 60% of VO2peak. 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 postprandial and abstained from caffeine for 12 h and from exercise and all medications for 24 h before the study. The second study day, for all male subjects, was at least 5 days and not more than 10 days after the first study day, providing more than adequate time for clearance of fexofenadine (half-life 1.15 h) and ranitidine (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.

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% VO2peak. 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.

H1- and H2-Receptor Blockade and Biochemical Analyses

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 ~1.15 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).

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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 insonated 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.
Femoral vascular conductance was calculated as flow for both legs/mean arterial pressure (expressed as ml/min/mHg). Brachial vascular conductance was calculated as flow for both arms/mean arterial pressure (expressed as ml/min/mHg).

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 to exercise were calculated from changes in hemoglobin and hematocrit by the method of Dill and Costill (7).

Data Analysis

The individual analyzing the data was blind regarding drug condition for each study day.

Statistics. The results were analyzed with a mixed-model ANOVA (within groups: drug vs. time; between groups: sex, trained status) with SAS (PROC MIXED, SAS v9.1, SAS Institute, Cary, NC). Differences were considered significant when \( P < 0.05 \). All values are reported as means \( \pm \) SE or means \( \pm \) SD.

RESULTS

Subject Characteristics

Subject characteristics are shown in Table 1. \( \dot{V}O_2 \text{peak} \) values were within the normal range for the sedentary population [sedentary men: 38.4 \( \pm \) 3.5 ml•kg\(^{-1}•\)min\(^{-1} \) (mean \( \pm \) SD); sedentary women: 27.5 \( \pm \) 6.5 ml•kg\(^{-1}•\)min\(^{-1} \) and for the endurance exercise-trained population (trained men: 58.4 \( \pm \) 3.8 ml•kg\(^{-1}•\)min\(^{-1} \); trained women: 42.9 \( \pm \) 5.5 ml•kg\(^{-1}•\)min\(^{-1} \) (\( P < 0.05 \) both trained groups vs. sedentary). Endurance-trained men and women also participated in a higher level of daily activity and frequency than their sedentary counterparts (\( P < 0.05 \)) as self-reported by all groups in the physical activity questionnaires (Table 1). These findings are also consistent with prior work where the population groups were also separated by training status (40).

Preexercise Hemodynamics

Preexercise hemodynamics are shown in Table 2. Supine resting heart rate and mean arterial pressure were not different within groups between control and \( H_1 \)- and \( H_2 \)-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% \( \dot{V}O_2 \text{peak} \). Average workloads are shown in Table 1 for each group. Heart rate reserve (heart rate reserve is defined as maximal heart rate achieved during \( \dot{V}O_2 \text{peak} \) testing minus the resting supine heart rate), heart rate, and mean arterial pressure were not different within groups between control and \( H_1 \)- and \( H_2 \)-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 \( H_1 \) and \( H_2 \)-receptor antagonists prevented the decrease in mean arterial pressure.
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 (Fig. 3; $P < 0.05$). 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

### Table 3. Exercise hemodynamics at 60% $\dot{V}O_2$peak

<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 Blockade</td>
<td>Control Blockade</td>
<td>Control Blockade</td>
<td>Control Blockade</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>145±3</td>
<td>141±3</td>
<td>140±5*</td>
<td>139±4</td>
</tr>
<tr>
<td>Heart rate reserve, %</td>
<td>69.3±3.1*</td>
<td>66.6±2.4</td>
<td>65.7±2.3*</td>
<td>64.7±2.1</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>93.6±5.7</td>
<td>96.4±3.4</td>
<td>94.3±2.4*</td>
<td>94.0±2.6</td>
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</tbody>
</table>

Values are means ± SE; $n = 7$ subjects for each group. *$P < 0.05$ vs. women within same training status.
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 H1- and H2-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 H1- and H2-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 ± 0.6 ng/ml, antagonists 4.3 ± 0.4 ng/ml; exercise: control 4.9 ± 0.5 ng/ml, antagonists 3.8 ± 0.5 ng/ml; both $P > 0.38$ vs. preexercise) or plasma (preexercise: control 0.4 ± 0.1 ng/ml, antagonists 0.3 ± 0.2 ng/ml; exercise: control 0.2 ± 0.1 ng/ml, antagonists 0.3 ± 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-receptor blockade.

Table 4. Cutaneous vascular conductance

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<tr>
<th></th>
<th>Sedentary Men</th>
<th>Control</th>
<th>Blockade</th>
<th>Sedentary Women</th>
<th>Control</th>
<th>Blockade</th>
<th>Trained Men</th>
<th>Control</th>
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<tr>
<td>Preexercise</td>
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<td>4.1±0.7</td>
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<td>1.3±0.4</td>
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<td>Postexercise 30 min</td>
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<td></td>
<td>6.2±2.8&lt;sup&gt;*&lt;/sup&gt;</td>
<td>4.5±1.3</td>
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<td></td>
<td>5.9±2.8&lt;sup&gt;*&lt;/sup&gt;</td>
<td>5.0±1.8</td>
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<td>2.6±0.6</td>
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<tr>
<td>Postexercise 90 min</td>
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<tr>
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<td>Postexercise 30 min</td>
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<td>13.1±4.3&lt;sup&gt;†&lt;/sup&gt;</td>
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<td>4.4±0.7</td>
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Values are means ± SE; \( n = 7 \) subjects for each group. CVC<sub>max</sub>, maximum cutaneous vascular conductance. \(* P < 0.05 \) vs. preexercise, \( † P < 0.05 \) vs. control at same time point.
tor antagonists in the sedentary and endurance exercise-trained men and women. In addition, the magnitude of the drop in blood pressure during recovery from exercise was blunted in all groups with the administration of H1- and H2-receptor antagonists.

Postexercise hypotension is characterized by a persistent rise in systemic vascular conductance that is not completely offset by increases in cardiac output (13). Forearm and calf vascular conductances increase in parallel with systemic vascular conductance; thus the vasodilation that underlies postexercise hyperemia and hypotension occurs so that vascular resistance is reduced for a given conductance after exercise was greater than that observed after presynaptic inhibition of norepinephrine release from sympathetic nerve activity (14). This suggests a mechanism involving a reduction in sympathetic nerve activity 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.

We have shown that blockade of H1 and H2 receptors attenuates the postexercise hyperemia and hypotension but that it only modestly attenuates systemic vascular conductance (i.e., overall peripheral vasodilation) (29, 31). Regulation of postexercise blood pressure is highly controlled, mediated by multiple and redundant mechanisms. For example, 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.

The mechanisms underlying postexercise hypotension in endurance trained men and women have not been elucidated. Senitko and coworkers (40) found that the peripheral vasodilation underlying postexercise hypotension was not present in endurance exercise-trained men, but it was present in endurance exercise-trained women. Our laboratory discovered that there is a histaminergic mechanism mediating the postexercise hyperemia in sedentary and normally active men and women (29, 31). The novel finding of this study is that 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).

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.

We have shown that blockade of H1 and H2 receptors attenuates the postexercise hyperemia and hypotension but that it only modestly attenuates systemic vascular conductance (i.e., overall peripheral vasodilation) (29, 31). Regulation of postexercise blood pressure is highly controlled, mediated by multiple and redundant mechanisms. For example, our laboratory has shown the vasodilation in the leg vasculature only accounts for 34% of the postexercise rise in systemic vascular conductance in a sedentary population (34). As such, it is not surprising that blocking skeletal muscle hyperemia did not abolish the rise in systemic vascular conductance. It could be that blocking the local skeletal muscle vasodilatory component of postexercise hypotension is not enough to overcome other changes in the regulation of peripheral vasodilation during recovery from exercise. Along these lines, local vasodilation is only one component of postexercise hypotension; another is a neural mechanism involving a reduction in sympathetic nerve activity (16, 27). It could be theorized that if the local vasodilation is blocked with administration of histamine antagonists, then the amount of sympathetic nerve activity might be decreased to other vascular beds in compensation. In support, the arterial baroreflex control of the skeletal muscle (16), renal (32, 34), and splanchnic (34) vascular beds appears to be reset to maintain a lower pressure following exercise. As such, it is likely that these vascular beds undergo baroreflex-mediated

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Table 5. Plasma and blood volume

<table>
<thead>
<tr>
<th></th>
<th>Sedentary Men</th>
<th></th>
<th>Trained Men</th>
<th></th>
<th>Sedentary Women</th>
<th></th>
<th>Trained Women</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Blockade</td>
<td>Control</td>
<td>Blockade</td>
<td>Control</td>
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<td>Control</td>
<td>Blockade</td>
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<td>n</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma volume, %Δ from preexercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>-15.9 ±1.5‡</td>
<td>-12.3 ±3.0*</td>
<td>-11.7 ±1.5‡</td>
<td>-13.0 ±1.3*</td>
<td>-11.8 ±3.6‡</td>
<td>-11.1 ±2.9‡</td>
<td>-12.0 ±1.8*</td>
<td>-16.4 ±1.2†‡</td>
</tr>
<tr>
<td>Postexercise 30 min</td>
<td>1.5 ±2.5</td>
<td>3.2 ±1.7</td>
<td>5.4 ±1.6‡</td>
<td>4.5 ±1.8§</td>
<td>1.1 ±2.9</td>
<td>2.3 ±1.5</td>
<td>8.1 ±7.6†‡</td>
<td>5.1 ±2.3†‡</td>
</tr>
<tr>
<td>Postexercise 60 min</td>
<td>0.6 ±2.3</td>
<td>4.3 ±1.2*</td>
<td>3.4 ±1.4</td>
<td>6.6 ±1.6§</td>
<td>0.2 ±2.0</td>
<td>2.0 ±1.8</td>
<td>7.2 ±2.5*</td>
<td>-0.4 ±2.4‡</td>
</tr>
<tr>
<td>Postexercise 90 min</td>
<td>-0.5 ±2.2</td>
<td>0.8 ±2.6</td>
<td>2.7 ±1.0§</td>
<td>1.9 ±1.5</td>
<td>-0.8 ±1.7</td>
<td>0.1 ±3.4</td>
<td>-6.7 ±8.4</td>
<td>-0.9 ±5.3</td>
</tr>
<tr>
<td>Blood volume, %Δ from preexercise</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>-8.6 ±1.4*</td>
<td>-6.3 ±2.2*</td>
<td>-7.0 ±0.7*</td>
<td>-8.0 ±0.9*</td>
<td>-7.1 ±2.9*</td>
<td>-8.7 ±1.6*</td>
<td>-7.0 ±1.6*</td>
<td>-11.0 ±2.6†‡</td>
</tr>
<tr>
<td>Postexercise 30 min</td>
<td>0.3 ±1.8</td>
<td>2.5 ±0.8*</td>
<td>3.1 ±1.2*</td>
<td>1.7 ±0.9§</td>
<td>1.4 ±2.7</td>
<td>0.2 ±0.9</td>
<td>6.3 ±5.5†‡</td>
<td>-4.5 ±2.1†‡</td>
</tr>
<tr>
<td>Postexercise 60 min</td>
<td>-0.3 ±1.4</td>
<td>2.6 ±1.1</td>
<td>1.3 ±0.7</td>
<td>2.9 ±1.0§</td>
<td>-0.4 ±1.7</td>
<td>-0.4 ±1.2</td>
<td>4.5 ±0.8</td>
<td>-1.9 ±2.7†</td>
</tr>
<tr>
<td>Postexercise 90 min</td>
<td>-0.4 ±1.8</td>
<td>1.3 ±1.7</td>
<td>1.0 ±0.4</td>
<td>1.0 ±1.0</td>
<td>0.0 ±1.4</td>
<td>-2.3 ±1.8</td>
<td>-4.3 ±6.4</td>
<td>-2.8 ±4.2</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. %Δ, percent change. *P < 0.05 vs. baseline (0% Δ), †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.
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 postexercise. All other groups showed no changes in cutaneous blood flow, consistent with prior studies (41). This could also account for the higher heart rate and reduction in stroke volume postexercise in the trained men. However, the increase in cutaneous vascular conductance was modest and unlikely to explain the magnitude of brachial blood flow augmentation postexercise. Furthermore, the histamine-receptor antagonists reduced blood flow to the brachial and femoral vascular beds but had no effect on the cutaneous vascular bed after exercise. In the end, without further understanding of the trigger for postexercise histamine-receptor activation it is unlikely we will be able to explain this population difference.

Have we identified the unknown vasodilator underlying postexercise hypotension? Histamine is the most likely candidate to bind to both H1 and H2 receptors; however, other compounds might be able to bind and activate both receptors. To date, there are no clear data to address this issue. Arguments for and evidence against histamine being the unknown vasodilator can be found. First, why would histamine be released in response to exercise? Physical stimuli such as vibration and heat, which occur during exercise, have been suggested to cause histamine release from mast cells (1). There is also evidence that sympathetic withdrawal can lead to histamine release (3, 5, 33, 35) and that sympathetic withdrawal is a component of postexercise hypotension (10, 16, 27). Second, are histamine levels increased during exercise? In previous studies and this study, we measured venous plasma and whole blood histamine concentrations and found no changes in response to exercise in sedentary, normally active, and endurance-trained men and women (29, 31). Are there other explanations that would explain why both H1- and H2-receptor antagonists can abolish the vasodilation and blunt hypotension after exercise? One rationalization for these conflicting observations is that exercise could increase the sensitivity of the H1 and H2 receptors to histamine. For example, it has been shown that a decreased pH can alter the H1 receptor’s binding site to allow for a greater sensitivity to histamine (11). An alternative explanation is that histamine could be released locally and cleared before significant spillover into the circulation. For example, postexercise hyperemia is absent in skin, splanchnic, and renal vascular beds, suggesting that histamine is not circulating systemically. There is reason to believe that histamine, the primary vasodilator contributing to postexercise hypotension, but we cannot say for certain. Further confirmation might depend on quantifying changes in interstitial histamine levels postexercise. Interstitial histamine concentrations would be of interest considering that histamine can be released 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.

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REFERENCES


