H₂-receptor-mediated vasodilation contributes to postexercise hypotension

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H₂-receptor-mediated vasodilation contributes to postexercise hypotension. J Appl Physiol 100: 67–75, 2006. First published September 1, 2005; doi:10.1152/japplphysiol.00959.2005.—The early (~30 min) postexercise hypotension response after a session of aerobic exercise is due in part to H₁-receptor-mediated vasodilation. The purpose of this study was to determine the potential contribution of H₂-receptor-mediated vasodilation to postexercise hypotension. We studied 10 healthy normotensive men and women (ages 23.7 ± 3.4 yr) before and through 90 min after a 60-min bout of cycling at 60% peak O₂ uptake on randomized control and H₂-receptor antagonist days (300 mg oral ranitidine). Arterial pressure (automated auscultation), cardiac output (acetylene washout) and femoral blood flow (Doppler ultrasound) were measured. Vascular conductance was calculated as flow/mean arterial pressure. Sixty minutes postexercise on the control day, femoral (Δ62.3 ± 15.6%, where Δ is change; P < 0.01) and systemic (Δ13.8 ± 5.3%; P = 0.01) vascular conductances were increased, whereas mean arterial pressure was reduced (Δ−6.7 ± 1.1 mmHg; P < 0.01). Conversely, 60 min postexercise with ranitidine, femoral (Δ9.4 ± 9.2%; P = 0.34) and systemic (Δ−2.8 ± 4.8%; P = 0.35) vascular conductances were not elevated and mean arterial pressure was not reduced (Δ−2.2 ± 1.3 mmHg; P = 0.12). Furthermore, postexercise femoral and systemic vascular conductances were lower (P < 0.05) and mean arterial pressure was higher (P = 0.01) on the ranitidine day compared with control. Ingestion of ranitidine markedly reduces vasodilation after exercise and blunts postexercise hypotension, suggesting H₂-receptor-mediated vasodilation contributes to postexercise hypotension.

POSTEXERCISE HYPOTENSION OCCURS after a single bout of dynamic exercise (20, 30, 37). Although mechanisms behind postexercise hypotension have not been fully elucidated, this phenomenon, in most subjects, is due to a persistent rise in peripheral vascular conductance that is not completely offset by increases in cardiac output (20, 23, 24), although endurance-trained men are an exception (48).

The mechanisms of the vasodilation underlying postexercise hypotension are just beginning to be revealed. Several studies have long been pointing to an unknown vasodilator as being largely responsible for the persistent vasodilation. First, despite clear evidence of reduced sympathetic outflow to skeletal muscle vascular beds in humans (16, 23) and rats (33), blockade of α-adrenergic receptors was unable to reproduce the magnitude of postexercise vasodilation in skeletal muscle (22). Second, despite evidence in support of vascular α-adrenergic hyperresponsiveness in rats (45), α₁- and α₂-adrenergic vascular responsiveness is intact in humans (21). Therefore, the possible involvement of several likely vasodilators has been studied in humans. Although nitric oxide contributes to postexercise vasodilation in rats (40), inhibition of nitric oxide synthase does not reduce the postexercise vasodilation in humans (22). Inhibition of cyclooxygenase also does not reduce the postexercise vasodilation in humans (35). Therefore, prostaglandins and nitric oxide do not seem to independently mediate postexercise hypotension in humans. However, our laboratory recently showed that with ingestion of a histamine 1 (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 (36). This begs the question, what is mediating the later stages (~60–90 min) of postexercise hypotension?

Histamine is stored and released by mast cells in most tissues and basophils in blood. Histamine can also be synthesized (but not stored) in some tissues by histidine decarboxylase. Histamine levels have been shown to increase during and after exercise (9, 15, 25), but it is unclear whether histamine contributes to exercise hyperemia. However, there does seem to be activation of H₁ receptors immediately (~30 min) after exercise (36). Physical stimuli such as vibration and heat have been suggested to cause histamine release from mast cells (2). Exercise might elicit histamine release via these stimuli. There is also evidence that sympathetic withdrawal can lead to histamine release (4, 7, 43, 46), and sympathetic withdrawal is a component of postexercise hypotension (16, 23, 33). Thus there are several potential scenarios that could lead to histamine release during or after exercise. Histamine can induce vasodilation by binding to H₁ receptors located on vascular endothelial cells or to histamine 2 (H₂)-receptors located on vascular smooth muscle cells. Several studies have shown a time course for differential vasodilation produced from H₁- and H₂-receptor activation (5, 10, 17, 41), where early vasodilation is due to H₁-receptor activation but a delayed and sustained vasodilation is due to H₂-receptor activation. This same time course could be plausible for the vasodilation underlying postexercise hypotension, because our laboratory has already shown H₁ receptors are responsible for the immediate postexercise hypotension response (~30 min) (36). Thus it seems likely H₂ receptors could account for the later response.

Therefore, the goal of this study was to determine the potential contribution of H₂-receptor-mediated vasodilation to postexercise hypotension in humans. We tested the hypothesis that the regional vasodilation in the leg vasculature during postexercise hypotension would be partially reversed by administration of ranitidine hydrochloride, a substance that selectively blocks H₂ receptors.

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

A total of 10 healthy, nonsmoking, normotensive subjects between the ages of 19 and 31 yr participated in this study (5 men; 5 women). On the basis of their exercise habits over the prior 12 mo, subjects were classified as “normally active” (no regular endurance activity). These subjects participated in <2 h of aerobic exercise per week. Subjects were taking no medication other than oral contraceptives. Female subjects had a negative pregnancy test on both the screening and study days.

Screening Visit

Subjects reported to the laboratory for a screening visit and cycle ergometer test at least 2 h postprandial and abstained from caffeine, alcohol, and exercise for 24 h before the screening visit. Subjects performed an incremental cycle exercise test (Lode Excaliber, Groningen, The Netherlands) consisting of 1-min workload increments to determine peak $O_2$ uptake ($V_{O_2\text{peak}}$). 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 an exhaustion within 8–12 min. Whole body $O_2$ 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 (6) 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 $O_2$ uptake of 60% of $V_{O_2\text{peak}}$. This workload was used on the 2 study days for the 60-min exercise bout. Subjects self-reported activity levels on two questionnaires (3, 31).

Study Visits

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 ranitidine [half-life ~2.6 h (18)]. Female subjects were studied during consecutive early follicular phases of the menstrual cycle or placebo phases of the oral contraceptive cycle.

Experimental Protocol

Subjects reported for parallel experiments on 2 separate days. The order of experiments was randomized between an H$_2$-receptor antagonist (ranitidine) and a control day. On study days, subjects were given water with or without 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% $V_{O_2\text{peak}}$. Exercise of this intensity and duration produces a sustained (~2 h) postexercise hypotension (20). During exercise, subjects received 15 ml of water for every 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 with the subjects in the supine position.

H$_2$-Receptor Blockade and Biochemical Analyses

H$_2$-receptors were blocked with 300 mg ranitidine HCl (brand name: Zantac; Pfizer Consumer Healthcare, Morris Plains, NJ). This amount of oral ranitidine has been shown to adequately block H$_2$ receptors with a peak plasma concentration at 2.2 h and a 2.6 h half-life. Responses are >90% inhibited within 1 h and remain inhibited 6 h after administration (8, 18). Ranitidine does not appear to cross into the central nervous system, have direct cardiovascular effects, or possess sedative actions (8). Blockade of H$_2$ receptors prevents the decrease in smooth muscle intracellular calcium levels that usually occurs with binding of histamine (8, 27). Blockade of H$_2$ 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 ~8°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 is expressed in nanograms per milliliter (IBL-America, Minneapolis, MN) (14). 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.

Additional Protocols

Sham study. To determine whether ranitidine caused a nonspecific vasoconstriction that could be superimposed on postexercise hypotension (masking the normal physiological response), we conducted a sham protocol on four of the subjects (2 men; 2 women). Subjects ingested the H$_2$-receptor antagonist and then laid supine for instrumentation. Measurements were taken for 30 min before and through 90 min after a 60-min bout of sham exercise (upright sitting). Baseline (preexercise), 30 min, 60 min, and 90 min postsham measurements included cardiac output, heart rate, arterial pressure, femoral and brachial blood flows. All presham and postsham measurements were made in the supine position.

Specificity test of ranitidine. To test the possibility that the reduction in the postexercise vasodilation with the H$_2$-receptor antagonist observed in the primary protocol was due to nonspecificity of ranitidine and antagonism of H$_1$ receptors, we conducted histamine skin prick tests on six subjects as a separate protocol. The histamine skin prick test is specific for H$_1$-receptor activation (13, 19, 47) and was administered on 2 different study days, separated by 5–9 days. On both study days, subjects underwent skin prick tests before and 120 min after ingestion of either 540 mg fexofenadine (H$_1$-receptor blocker) or 300 mg ranitidine (H$_2$-receptor blocker). Drug administration (fexofenadine vs. ranitidine) was randomized across the 2 study days. Wheal and flare areas were measured during the histamine skin prick tests to determine the effect of the two histamine-receptor blockers. The histamine skin prick test was administered by placing a droplet of histamine dihydrochloride (10 mg/ml) on the skin of the anterior forearm and breaking the skin through the droplet with a purpose-built sterile lancet (1.2-mm tip; Quintip, Hollister-Stier, Spokane, WA). After 1 min, the remaining droplet was wiped off. After 10 min, wheal and flare areas were imaged for offline analysis by computer planimetry (13, 19, 47).

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 (28, 35). This method allows 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 nonbreathing valve. During the washin phase, breath-by-breath acetylene and helium uptake were measured by a respiratory mass spectrometer (Marquette GMA 1100), and tidal volume was measured via a pneumotach (model 3700, Hans Rudolph, Kansas City, MO) linearized by the technique of Yeh et al. (51) 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 (28). 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 doubled to represent both legs or arms, respectively (expressed as ml/min). Femoral vascular conductance 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).

Skin blood flow. Red blood cell flux was used as an index of skin blood flow via laser-Doppler flowmetry (model 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 normalized to the maximal values achieved during local heating to 43°C (29·mmHg⁻¹).

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 (12).

Data Analysis

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

Statistics. Because there were no discernable differences between men and women, data from the two groups were combined for statistical analysis. The results were analyzed with a repeated-measures two-way ANOVA (drug vs. time). Significant effects were further tested with Fisher’s least significant difference test, and differences were considered significant when P < 0.05. All values are reported as means ± SE.

RESULTS

Subject characteristics are shown in Table 1. VO₂ peak values were within the normal range for this population [38.7 ± 7.54 ml·kg⁻¹·min⁻¹ (means ± SD)].

Preexercise Hemodynamics

Supine resting heart rate was 63.0 ± 2.9 beats/min on the control day and 61.0 ± 2.5 beats/min on the H₂-receptor antagonist day (ranitidine day) (Table 2). Resting mean arterial pressure was 80.2 ± 3.2 mmHg on control day and 80.0 ± 3.0 mmHg on ranitidine day. There were no differences in resting heart rate and mean arterial pressure values between study days (P > 0.20).

Exercise

The goal was to have subjects exercise for 60 min at 60% VO₂ peak. On both days, the average workload was 109.4 ± 6.0 W. On the control day, heart rate was 143.8 ± 3.3 beats/min during exercise. This represented, on average, 65.9 ± 1.3% heart rate reserve (heart rate reserve is defined as maximal heart rate achieved during VO₂ peak testing minus the resting supine heart rate) and is consistent with the target workload.

On the ranitidine day, heart rate was 141.2 ± 3.6 beats/min during exercise. This represented, on average, 64.9 ± 2.3% heart rate reserve and is consistent with the target workload. There were no differences in percent heart rate reserve (P = 0.61) or the arterial pressure response to exercise (control 89.9 ± 2.8 mmHg; ranitidine 88.6 ± 3.1 mmHg; P = 0.34) between the 2 study days.

Postexercise Hemodynamics

Table 2 shows postexercise vs. preexercise hemodynamics on both study days. Cardiac output was higher 30 min postexercise compared with preexercise on the control day (P < 0.05). There were no differences in heart rate, stroke volume, and cardiac output between the 2 study days (P > 0.23). Figure 1 shows mean arterial pressure, systemic vascular conductance, femoral vascular conductance, and brachial vascular conductance values preexercise and through 90 min postexercise on both study days. Mean arterial pressure was reduced during the entire period of recovery from exercise on the control day (P < 0.05; Fig. 1A). On the ranitidine day, mean arterial pressure was reduced 30 min after exercise but at 60 and 90 min postexercise had returned to baseline levels (both P > 0.11; Fig. 1A). Systemic vascular conductance was increased during recovery from exercise on the control day (P < 0.05), whereas this rise was blunted on the ranitidine day (P > 0.33; Fig. 1B). Femoral vascular conductance was increased during recovery from exercise at all time points on the control day and as well as 30 min postexercise on the ranitidine day (P < 0.05; Fig. 1C). However, this rise was blunted compared with the control day, and at 60 through 90 min postexercise the conductance had returned to baseline levels (P > 0.33; Fig. 1C). Brachial vascular conductance increased after exercise on the control day (P < 0.05), and this rise was blunted with ranitidine (P > 0.30; Fig. 1D).

Figure 2 shows the changes in mean arterial pressure and systemic, femoral, and, brachial vascular conductances from baseline to 30, 60, and 90 min postexercise. Mean arterial

<table>
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<th>Table 1. Subject characteristics</th>
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<tr>
<td>Age, yr</td>
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<tr>
<td>Height, cm</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<td>VO₂ peak, ml·kg⁻¹·min⁻¹</td>
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<td>Workload at 60% of VO₂ peak, W</td>
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<td>Baecke sport index, arbitrary units</td>
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<td>Index of physical activity, MET·h/wk</td>
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Values are means ± SD; n = 10 subjects. VO₂ peak, peak oxygen consumption; MET, metabolic equivalents.
pressure was reduced ~4–6 mmHg after exercise at all time points on the control day but only at 30 min postexercise on the ranitidine day. Furthermore, the drop was less at 60 and 90 min postexercise on the ranitidine day than on the control day (P < 0.05 vs. control day; Fig. 2A). Systemic vascular conductance was increased by ~15% after exercise on the control day. This rise was blunted on the ranitidine day (P = 0.056 vs. control day; Fig. 2B). Femoral vascular conductance was increased by ~60% on the control day. This rise was blunted on the ranitidine day (P < 0.05 vs. control; Fig. 2C). Brachial vascular conductance was increased by ~20–30% after exercise on the control day. This response tended to be less on the ranitidine day (P > 0.14; Fig. 2D).

Skin Blood Flow

Table 2 shows forearm and thigh cutaneous vascular conductance, presented relative to maximal values. Thirty minutes after exercise, values at both sites were similar to preexercise (P > 0.17), and there were no differences between study days (P > 0.22).

Plasma and Blood Volume

During exercise, both plasma volume (Δ −10.9 ± 1.1% control and Δ −11.3 ± 2.3% ranitidine, where Δ is change; both P < 0.05) and blood volume (Δ −6.6 ± 0.8% control and Δ −6.6 ± 1.7% ranitidine; both P < 0.05) decreased from baseline. At 30 min postexercise on the control day, both plasma volume (Δ7.9 ± 1.9%; P < 0.05 vs. preexercise) and blood volume (Δ4.7 ± 1.6%; P < 0.05 vs. preexercise) had increased above baseline levels and remained elevated throughout the remaining 90 min of the protocol (plasma volume = Δ7.8 ± 1.1% 60 min postexercise and Δ7.3 ± 1.7% 90 min postexercise, both P < 0.05 vs. preexercise and blood volume = Δ4.4 ± 1.0% 60 min postexercise and Δ3.9 ± 1.2% 90 min postexercise, both P < 0.05 vs. preexercise). In contrast, 30 min postexercise on the ranitidine day, both plasma (Δ5.7 ± 2.9%; P = 0.12 vs. preexercise) and blood volumes (Δ2.7 ± 2.0%; P = 0.20 vs. preexercise) had returned to and remained at preexercise levels throughout the rest of the protocol. However, there were no differences in plasma (P > 0.19) or blood volume (P > 0.10) changes between the 2 study days.

Histamine Concentration

Whole blood histamine concentrations did not differ between preexercise, end of exercise, or any of the postexercise measurements (all time points P > 0.33 vs. preexercise; Fig. 3A). There were no differences between study days (P > 0.38).

Similarly, plasma blood histamine concentrations did not differ between preexercise, end of exercise, or any of the postexercise measurements (all time points P > 0.20 vs. preexercise; Fig. 3B). There were no differences between study days (P > 0.17).

Sham Study

The four subjects that completed the sham protocol showed no differences in mean arterial pressure (P > 0.26), systemic vascular conductance (P > 0.37), femoral vascular conductance (P > 0.18), and brachial vascular conductance (P > 0.32) throughout the sham protocol (Table 3).

Specificity Test of Ranitidine

Table 4 shows wheal and flare areas for each histamine skin prick test, before and after fexofenadine or ranitidine administration. Fexofenadine diminished both the wheal and flare responses to the histamine prick test (P < 0.05), whereas ranitidine had no effect on the wheal or flare responses (P > 0.22).

DISCUSSION

The early postexercise hypotension seen at 30 min after a single bout of aerobic exercise is mediated in large part by an H1-receptor-mediated vasodilation (36). The goal of this study was to determine whether H2 receptors also mediate this postexercise vasodilation in humans. In agreement with our hypothesis, we found that administering the selective antagonist of H2 receptors, ranitidine, resulted in a reduction in the
Fig. 1. Mean arterial pressure (A), systemic vascular conductance (B), femoral vascular conductance (C), and brachial vascular conductance (D) preexercise and at 30 min (Post-30), 60 min (Post 60), and 90 min (Post-90) postexercise. Values are means ± SE; n = 10 subjects. *P < 0.05 vs. preexercise, †P < 0.05 vs. control day at same time point.

Fig. 2. Absolute change (△) in mean arterial pressure and percent change (%△) in systemic, femoral, and brachial vascular conductances from preexercise to 30, 60, and 90 min postexercise. A: absolute decrease in mean arterial pressure. B: %rise in systemic vascular conductance. C: %rise in femoral vascular conductance. D: %rise in brachial vascular conductance. Values are means ± SE; n = 10. *P values are ranitidine vs. control day.
Systemic vascular conductance, ml/min 71.7
Stroke volume, ml/beat 4.5
Cardiac output, 1/min 61.2
Brachial vascular conductance, ml/min 91.9
Femoral vascular conductance, ml/min 466
Heart rate, beats/min 11006
Brachial blood flow, ml/min 11006
Femoral blood flow, ml/min 11006
Mean arterial pressure, mmHg 87.4

Sham hemodynamics

Table 3. Sham hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Preexercise</th>
<th>Post 30</th>
<th>Post 60</th>
<th>Post 90</th>
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<tr>
<td>Mean arterial pressure, mmHg</td>
<td>87.4 ± 3.9</td>
<td>88.1 ± 4.5</td>
<td>86.8 ± 5.1</td>
<td>88.4 ± 5.1</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>61.2 ± 4.1</td>
<td>56.5 ± 3.7</td>
<td>56.3 ± 4.2</td>
<td>58.4 ± 3.7</td>
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<td>Cardiac output, 1/min</td>
<td>4.5 ± 0.5</td>
<td>4.2 ± 0.4</td>
<td>4.3 ± 0.5</td>
<td>4.3 ± 0.4</td>
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<tr>
<td>Stroke volume, ml/beat</td>
<td>71.7 ± 11.8</td>
<td>70.0 ± 10.8</td>
<td>78.1 ± 13.2</td>
<td>73.9 ± 7.6</td>
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<td>Systemic vascular conductance, ml/min/mmHg⁻¹</td>
<td>51.4 ± 4.6</td>
<td>48.7 ± 4.0</td>
<td>49.8 ± 6.2</td>
<td>48.9 ± 5.2</td>
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<tr>
<td>Femoral blood flow, ml/min</td>
<td>466 ± 141</td>
<td>482 ± 128</td>
<td>540 ± 160</td>
<td>525 ± 165</td>
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<td>Femoral vascular conductance, ml/min/mmHg⁻¹</td>
<td>5.21 ± 1.40</td>
<td>5.37 ± 1.30</td>
<td>6.07 ± 1.60</td>
<td>5.82 ± 1.60</td>
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<tr>
<td>Brachial blood flow, ml/min</td>
<td>91.9 ± 2.9</td>
<td>90.3 ± 4.1</td>
<td>91.3 ± 8.7</td>
<td>84.5 ± 8.1</td>
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<tr>
<td>Brachial vascular conductance, ml/min/mmHg⁻¹</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.97 ± 0.1</td>
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Values are means ± SE; n = 4 subjects.

vasodilation after exercise and markedly blunted the magnitude of postexercise hypotension, particularly over the 60- to 90-min postexercise period.

Postexercise hypotension is characterized by a persistent rise in systemic vascular conductance that is not completely offset by increases in cardiac output (20). Forearm and calf vascular conductances are increased in parallel with systemic vascular conductance; thus the vasodilation that underlies postexercise hypotension is not restricted to the sites of active skeletal muscles (22, 34). Vasodilation is largely in skeletal muscle vascular beds with little or no contribution from skin, splanchnic, or renal circulations (44, 49). This peripheral vasodilation includes both a neural and a vascular component. Previously, Halliwill et al. (23) have shown in humans that the baroreflex is reset to a lower pressure after exercise, creating a reduction in sympathetic vasoconstrictor outflow. In addition, vascular responsiveness to sympathetic vasoconstrictor outflow is impaired so that vascular resistance is reduced for a given level of sympathetic nerve activity, independent of changes in α-adrenergic receptor responsiveness (21). This suggests a presynaptic inhibition of norepinephrine release from sympathetic vasoconstrictor nerves after exercise. However, in another study by Halliwill et al. (22), the increase in vascular conductance after exercise was greater than that observed after α-adrenergic receptor blockade, suggesting the existence of a superimposed vasodilator signal. Our laboratory recently showed that part of the postexercise hyperemia response could be explained by an H₂-receptor-mediated vasodilation (36). Our present study shows that H₂-receptor-mediated vasodilation is also involved.

Histamine is stored and released by mast cells within most tissues and by basophils in the blood. It can also be synthesized in non-mast cell tissues such as cells of the epidermis, cells in gastric mucosa, neurons within the central nervous system, and cells in regenerating tissues, by the actions of l-histidine decarboxylase (8). Once released, histamine binds to several histamine-receptor subtypes. H₁ receptors are predominately located on vascular endothelial cells and cause vasodilation via formation of local vasodilators, such as nitric oxide and prostacyclin. H₂ receptors are located predominately on smooth muscle cells and cause vasodilation by decreasing intracellular calcium levels (8, 27). Histamine 3 (H₃) receptors have been suggested to be located throughout tissues on presynaptic nerve terminals and may cause vasodilation by inhibiting norepinephrine release (38) and/or by decreasing intracellular calcium levels (8).

Numerous substances and certain conditions have been suggested to cause mast cells and basophils to release histamine (2). It has been suggested that exercise causes histamine release; however, this is difficult to assess in humans because red blood cells actively take up histamine (9). Histamine levels have been measured in arterial and venous whole blood as well as venous plasma during and after high-intensity exercise (9, 15, 25, 26, 39). However, these studies do not agree on an

Fig. 3. Whole blood (A) and plasma (B) histamine concentrations at preexercise (Pre), end of exercise, and at 30, 60, 90 and min postexercise. Values are means ± SE; n = 10 subjects.
adequate method for collecting and analyzing histamine. In the present study, we measured venous plasma and whole blood histamine concentrations and found no changes in response to exercise. Nonetheless, both H1- and H2-receptor antagonists can blunt the vasodilation and hypotension after exercise. One explanation for these conflicting observations is that exercise increases the sensitivity of the H1 and H2 receptors to histamine. An alternative explanation is that histamine is released locally and cleared before significant spillover into the circulation. Have we identified the unknown vasodilator underlying postexercise hypotension? Ranitidine is a highly selective H2-receptor antagonist (8). Histamine is the most likely candidate to bind to H2 receptors; however, other compounds might be able to bind and activate H2 receptors. Therefore, we cannot say with certainty that histamine is the unknown vasodilator. However, we have now demonstrated that both H1 and H2 receptors are contributors to postexercise hypotension. This is strong evidence that histamine is the primary vasodilator. Further confirmation might depend on quantifying changes in interstitial histamine levels. Nonetheless, histamine does appear to be the most likely candidate at this time.

Our laboratory has previously shown that H1 receptors are involved in the early (~30 min) stages of postexercise hypotension. This present study examined the role of H2 receptors; it seems as though both H1 and H2 receptors mediate postexercise hypotension. The stimulation of H1 receptors plays a more significant role in the early postexercise hypotension (~30–60 min), whereas H2 receptors become involved in the later stages of postexercise hypotension (~60–120 min). This would be consistent with the known pharmacokinetics of these receptors. When H1 receptors are stimulated, the vasodilation produced has a rapid onset and is short lived; however, H2 receptors produce an extended period of vasodilation after a slow onset (8). It is possible that additional receptor subtypes are also involved in postexercise hypotension. H3 receptors are located throughout the periphery and could play a role in inhibiting presynaptic release of norepinephrine (38). Along these lines, Halliwill et al. (23) showed that vascular responsiveness to sympathetic vasoconstrictor outflow is impaired postexercise so that vascular resistance is reduced for a given level of sympathetic nerve activity, independent of changes in α-adrenergic receptor responsiveness. Thus, if H1 receptors are stimulated during and after exercise, they could explain this observation of impaired vascular transduction. Because of the lack of an H3-receptor antagonist for use in human subjects, we can only speculate at this time regarding the role of H3 receptors. However, it is plausible that the release of histamine would also affect this receptor.

Alternative Explanations

Wong and coworkers (50) found that H2 receptors do not contribute to the rise in skin blood flow during whole body heating, and our laboratory has previously shown that skin blood flow does not contribute to postexercise hypotension under thermoneutral conditions (49). Nonetheless, we have considered the possibility that a reduction in cutaneous vascular conductance contributes to the decrease in femoral and brachial vascular conductances with ranitidine. In the present study, we found no differences in skin blood flow between the 2 study days, despite a reduction in both femoral and brachial artery blood flow with the H2-receptor antagonist. These results suggest that the reduction in the magnitude of postexercise hypotension with ranitidine is not due to decreased cutaneous vasodilation but that it results from a decrease in skeletal muscle vasodilation.

We have also considered the possibility that ranitidine caused vasoconstriction that is superimposed on the postexercise hypotension response. To address this concern, we conducted a time control study (sham exercise) in four of the subjects and found no differences in mean arterial pressure or systemic, femoral, and brachial vascular conductances across time. Thus it seems unlikely that the effect on postexercise hypotension is due to the H2-receptor antagonist causing nonspecific vasoconstriction.

Another plausible explanation for these data is that the H2-receptor blocker is nonspecific and is blocking H1 receptors. If so, our data would be nothing more than a repeat of our prior investigation with an H1-receptor antagonist (36). To address this issue, we used a common clinical tool (the histamine skin prick test) to assess the specificity of ranitidine for H2 receptors. This test is used clinically to test the efficacy of H1-receptor antagonists. We found the flare response was eliminated only after administration of an H1-receptor antagonist and not after administration of ranitidine. Thus administering ranitidine, in the dose we used, does not appear to cause any antagonism of H1 receptors.

Perspectives

Our findings from this present study and our prior work (36) suggest that H1 and H2 receptors both play important roles in the postexercise response. Anrep and Barsoum (1) first suggested that histamine caused skeletal muscle vasodilation in the 1930s, when they noted an increase in histamine concentration in venous blood in response to muscle contractions and occlusions in dogs (1). However, later studies using first-generation histamine-receptor blockers concluded that there was no contribution of histamine to reactive or exercise hyperemia (11, 43). Our studies are unique from these earlier studies in that we focus on recovery from exercise and use second-generation histamine-receptor antagonists in human subjects. The substantial contribution of histamine receptors to postexercise hyperemia resurrects earlier notions that histamine may be involved in minute-to-minute physiological regulation of skeletal muscle blood flow. If so, mechanisms of its regulation need to be identified, and other situations in which histamine receptors play a role in blood flow may be uncovered.
The clinical “goal” of postexercise hypotension research is tightly coupled to the notion that daily exercise will translate into prevention and/or treatment of hypertension. Recent American College of Sports Medicine guidelines go so far as to suggest postexercise hypotension be used as an incentive to demonstrate that exercise will benefit those with hypertension (42). A link between postexercise hypotension and long-term benefits of exercise such as amelioration of hypertension remains unproven at this time, but our present findings raise the question, what happens in hypertensive patients who also take over-the-counter and prescription drug treatments for allergies or heartburn? Does this challenge the antihypertensive benefits of exercise by altering the normal blood pressure response to exercise?

At the other end of the clinical spectrum, histamine antagonists might benefit patients who suffer from exercise-related vasovagal syncope. In some of these individuals postexercise hypotension is exaggerated and leads to symptoms of orthostatic intolerance, including syncope (32). As histamine receptors play a significant role in the “normal” postexercise hypotension response, histamine-receptor antagonists might be beneficial for patients who suffer from exercise-related vasovagal syncope.

In conclusion, ingestion of an H2-receptor antagonist markedly reduces vasodilation after exercise and blunts postexercise hypotension. These data suggest an H2-receptor-mediated vasodilation contributes to postexercise hypotension in humans.

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