The effect of histamine on the human fingertip circulation

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Summary

1. The effect of intra-arterial histamine on fingertip blood flow (FBF) and vascular resistance (FVR) was studied in normal subjects during reflex sympathetic vasoconstriction induced by body cooling and vasoconstriction caused by intra-arterial noradrenaline.

2. In a room at 20°C, FBF increased from $15.3 \pm 3.5$ (sn) to $28.3 \pm 5.5$ ml min$^{-1}$ 100 ml$^{-1}$ of tissue and FVR decreased from $23.7 \pm 1.7$ to $11.9 \pm 0.9$ mmHg · ml min$^{-1}$ 100 ml$^{-1}$ ($P < 0.01$) during infusions of histamine (0.5-4 µg/min) in 14 subjects. In nine of these subjects, the disappearance half times of local injections of Na$^{131}$I were measured and decreased from $19.8 \pm 10.9$ to $12.9 \pm 7.3$ min during histamine infusions, indicating an increase in nutritional flow. Arteriovenous shunt flow was also probably affected, for increases in FBF were sometimes large and FBF increased without a change in the radioisotope half time in two subjects.

3. Neither cimetidine nor pyrilamine (mepyramine) consistently prevented the FBF responses to histamine. Administration of both antihistamines together attenuated the response.

4. During noradrenaline infusions in four subjects, a large increase in FBF ($8.9 \pm 10.9$ to $39.0 \pm 8.2$ ml, $P < 0.005$) occurred at the smallest dose (0.5 µg/min) of histamine.

5. It is concluded that histamine can vasodilate fingertips and increase nutritional blood flow during reflex sympathetic vasoconstriction. This vasodilatation may be mediated via both histamine H$_1$ and H$_2$ receptors.

Key words: arteriovenous anastomoses, cimetidine, fingertip blood flow, histamine, mepyramine, nutritional blood flow, pyrilamine.

Abbreviations: FBF, fingertip blood flow; FVR, fingertip vascular resistance.

Introduction

The physiological role of histamine in circulatory responses has been elucidated in only the last decade. It is known to be important in anaphylactic and allergic reactions and in gastric secretion, but now has been shown to be involved in active reflex dilatation in skeletal muscle [1]. In man, histamine has been shown to be a potent vasodilator of forearm and hand blood vessels [2]. Its actions on the fingertip circulation, where both arteriovenous (a-v) anastomoses and nutritional vascular beds are present, have not been studied.

Until our demonstration of a digital β-adrenergic vasodilator mechanism [3], vasodilatation in the fingertip was considered to occur only by withdrawal of sympathetic nerve activity. However, this β-adrenoceptor activity affected only a-v shunt flow and did not cause vasodilatation when reflex sympathetic vasoconstriction was induced. In studying the physiological control of finger blood flow and seeking mechanisms that could mediate vasodilatation, we found that histamine did dilate fingertip blood vessels during reflex vasoconstriction induced by total body cooling. This study determines the effect of histamine on total fingertip and nutritional blood flows and examines the role of histamine H$_1$ and H$_2$ selective antagonists on the response to histamine in the fingertip circulation.

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Methods

Twenty-nine studies were performed in normal subjects. All studies were approved by the Institutional Review Board for Human Studies, and subjects gave informed consent. Subjects were supine, covered only with a hospital gown in a room at 20°C for 1 h in order to induce reflex sympathetic vasoconstriction before measurements were started. Total fingertip blood flow (FBF) was measured by air-displacement venous occlusion plethysmography in the same finger of both hands. The hands and arms were positioned slightly above heart level. The plethysmographs consisted of finger cups sealed with caulking compound to the fingertips beyond the distal interphalangeal joints. A 25 mm wide pneumatic cuff was applied proximally to the finger cups. The lowest venous occlusion pressure required to obtain the maximal rate of increase in fingertip volume was determined and used throughout each study (average 56 mmHg). Changes in fingertip volume were detected by Sanborn pressure transducers (268A) connected by stiff rubber tubing to the finger cup outlets. The systems were calibrated by recording the pressure increase which occurred upon introduction of 0.1 ml of air. FBF was derived from the initial rate of rise in fingertip volume occurring with venous occlusion. The volume of the fingers within the finger cup was determined by water displacement to express blood flow in ml min⁻¹ 100 ml⁻¹ of tissue.

At the beginning of each study, an 18-gauge catheter was placed in the brachial artery of the test arm and maintained patent with 0.5 ml/min infusion of 0.9% sodium chloride solution (saline). The other arm served as a control. Drugs were dissolved in saline just before use and delivered intra-arterially by constant infusion pumps (Harvard Apparatus Co.) at 0.5-2 ml/min. Five per cent glucose in water was used as the noradrenaline solvent.

When plethysmographic measurements indicated stable blood flow in the cool room, histamine phosphate (Lilly, 0.5-4 µg/min) was infused. In these studies, the histamine dose was increased every 4 min until an increase in FBF was apparent or a dose of 4 µg/min was reached. In seven experiments, 25 mg of pyrilamine maleate (Sigma Chemical Co.) (mepyramine) was infused in the brachial artery over a 5 min period and, after 15 min, histamine infusions were repeated. In five experiments, 150 mg of cimetidine hydrochloride (Smith, Kline and French) was given by the same protocol. In three subjects, both antihistamines were given with histamine infusions after each drug.

In nine subjects, nutritional blood flow as reflected by the radioisotope disappearance rate was measured simultaneously with plethysmographic flow measurements in the test arm. Approximately 0.01 ml of Na¹³¹I in saline was injected with a 27-gauge needle into the skin of the pad of the fingertip adjacent to the finger with the plethysmograph. The disappearance rate was monitored by a scintillation probe, ratemeter (time constant = 5 s) and linear recorder. The scintillation probe contained a thallium-activated sodium iodide crystal, 2.5 x 2.5 cm. The dose of radioisotope was 2 µCi. Baseline disappearance rates were determined for 5-8 min and then intraarterial infusions of histamine were administered. During histamine infusions, the disappearance rates were followed for at least 4 min at each dose and for 5 min after termination of the drug infusion. Radioisotope activity was plotted on semi-logarithmic paper after subtraction of the background counts, and expressed as half-times.

In four subjects, the effect of histamine on the finger vasoconstriction induced by intra-arterial noradrenaline (levarterenol bitartrate, Winthrop, 0.125-0.5 µg of base/min) was studied in a room at 24°C. After initiation of infusion of noradrenaline, FBF reached a stable level within 4 min; then five measurements of FBF over 2 min were obtained and averaged. Histamine (0.5 µg/min) was then infused and, after an increase in blood flow had occurred, flows were obtained over a 4 min period and averaged.

Systemic blood pressure was measured by the sphygmonanometric method with each set of control flows and every 2 min during drug infusion. Pulse rates were counted at the same time. Mean blood pressure was calculated by adding one-third of the pulse pressure to diastolic pressure. Finger vascular resistance (FVR) was calculated by dividing mean blood pressure by average blood flow and expressed as mmHg · ml min⁻¹ 100 ml⁻¹ of tissue (units).

Since FBF often fluctuates spontaneously and widely in both hands, an estimate of the actual effect of histamine was calculated by the formula [4] $E = Ab/a$, where $E$ is expected FBF or FVR (if no drug effect), $A$ is pre-drug FBF or FVR in test hand, $b$ is FBF or FVR in control hand during drug infusion and $a$ is pre-drug FBF or FVR in control hand.

Whenever possible, the 'expected' FBF or FVR in the test finger, if no drug effect occurred, was calculated by this method and compared with the actual value obtained during the drug infusion. Statistical analyses were made by the Wilcoxon signed rank test or with Student’s t-test for paired
Results

After cooling, FBF, not adjusted for the control finger, was $15.3 \pm 3.55$ and increased with histamine infusions to $28.3 \pm 5.9$ ml min$^{-1}$ 100 ml$^{-1}$ of tissue ($P < 0.01$) (Table 1). FVR decreased from $23.7 \pm 17.7$ to $11.9 \pm 9.9$ units ($P < 0.01$).

In 11 of these 14 subjects who had flows measured in a finger of the opposite hand, the expected FBF during histamine infusions was $22.7 \pm 53.0$ and the observed FBF was $38.4 \pm 62.7$ ml min$^{-1}$ 100 ml$^{-1}$ of tissue ($P < 0.009$). The expected FVR was $26.0 \pm 18.0$ and the observed FVR was $12.1 \pm 11.0$ units ($P < 0.009$).

In nine of the above experiments, radioisotope disappearance rates were measured before and during histamine infusion in a finger adjacent to the plethysmograph (Table 2). The half times averaged $19.8 \pm 10.9$ before drug and $11.9 \pm 7.3$ min during histamine infusion ($P < 0.009$). The half times average of $19.6 \pm 11.2$ min after histamine infusion did not differ significantly from that before the drug ($P > 0.05$). In two of these subjects, radioisotope disappearance rates showed no change during histamine infusion even though FBF increased.

Ten subjects received pyrilamine via the brachial artery. No significant change in FBF ($7.5 \pm 6.5$ to $5.8 \pm 4.8$ ml min$^{-1}$ 100 ml$^{-1}$ of tissue, $P > 0.05$) or FVR ($21 \pm 16.7$ to $29.8 \pm 22.7$ units, $P > 0.05$) occurred during the drug infusion. In seven subjects, histamine infusion ($0.5-2.0 \mu g$ min$^{-1}$) was given before and 15 min after the pyrilamine infusion (Table 3). The average change in FBF with histamine was $4.3 \pm 5.6$ before and $4.1 \pm 6.4$ ml min$^{-1}$ 100 ml$^{-1}$ of tissue after pyrilamine ($P > 0.05$); FVR changes were $9.5 \pm 7.8$ and $7.0 \pm 6.4$ units respectively ($P > 0.05$). Three of the seven subjects did not have an increase in FBF with histamine ($0.5-1 \mu g$ min$^{-1}$) after pyrilamine;

### TABLE 1. Effect of intra-arterial infusion of histamine on fingertip circulation

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dose of histamine (H: \mu g/min)</th>
<th>FBF (test finger)</th>
<th>FVR (test finger)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before H</td>
<td>During H</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>2.4</td>
<td>4.4</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>9.7</td>
<td>16.5</td>
</tr>
<tr>
<td>13</td>
<td>0.5</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>25.1</td>
<td>43.0</td>
</tr>
<tr>
<td>10</td>
<td>1.0</td>
<td>2.5</td>
<td>3.8</td>
</tr>
<tr>
<td>12</td>
<td>1.0</td>
<td>3.1</td>
<td>7.9</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>8.4</td>
<td>38.2</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>4.5</td>
<td>6.5</td>
</tr>
<tr>
<td>9</td>
<td>2.0</td>
<td>4.8</td>
<td>18.7</td>
</tr>
<tr>
<td>11</td>
<td>2.0</td>
<td>7.4</td>
<td>8.3</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>136.7</td>
<td>217.1</td>
</tr>
<tr>
<td>7</td>
<td>4.0</td>
<td>1.1</td>
<td>20.9</td>
</tr>
<tr>
<td>8</td>
<td>4.0</td>
<td>3.5</td>
<td>4.8</td>
</tr>
<tr>
<td>14</td>
<td>4.0</td>
<td>2.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>15.3±35.5</td>
<td>28.3±55.9</td>
</tr>
</tbody>
</table>

* No control finger measurements.

### TABLE 2. Effect of intra-arterial infusion of histamine on fingertip radioisotope disappearance rates

<table>
<thead>
<tr>
<th>Subject</th>
<th>Na$^{131}$I half times (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before H</td>
</tr>
<tr>
<td>1</td>
<td>42.5</td>
</tr>
<tr>
<td>2</td>
<td>11.3</td>
</tr>
<tr>
<td>3</td>
<td>16.5</td>
</tr>
<tr>
<td>4</td>
<td>9.6</td>
</tr>
<tr>
<td>5</td>
<td>17.2</td>
</tr>
<tr>
<td>6</td>
<td>26.2</td>
</tr>
<tr>
<td>7</td>
<td>8.5</td>
</tr>
<tr>
<td>8</td>
<td>18.1</td>
</tr>
<tr>
<td>9</td>
<td>28.0</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19.8±10.9</td>
</tr>
</tbody>
</table>
TABLE 3. Effect of intra-arterial histamine on fingertip blood flow and vascular resistance before and after pyrilamine

<table>
<thead>
<tr>
<th>Pyrilamine (dose of histamine)</th>
<th>FBF Expected</th>
<th>FBF Observed</th>
<th>FVR Expected</th>
<th>FVR Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before (0.5 μg/min)</td>
<td>9.7</td>
<td>16.5</td>
<td>10.3</td>
<td>6.1</td>
</tr>
<tr>
<td>After</td>
<td>2.7</td>
<td>4.0</td>
<td>41.9</td>
<td>28.8</td>
</tr>
<tr>
<td>Before (0.5 μg/min)</td>
<td>21.8</td>
<td>26.7</td>
<td>3.9</td>
<td>3.2</td>
</tr>
<tr>
<td>After</td>
<td>4.5</td>
<td>17.0</td>
<td>20.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Before (0.5 μg/min)</td>
<td>0.8</td>
<td>0.9</td>
<td>93.0</td>
<td>85.5</td>
</tr>
<tr>
<td>After</td>
<td>1.9</td>
<td>2.5</td>
<td>43.7</td>
<td>33.2</td>
</tr>
<tr>
<td>Before (0.5 μg/min)</td>
<td>1.8</td>
<td>2.4</td>
<td>43.9</td>
<td>32.9</td>
</tr>
<tr>
<td>After</td>
<td>0.8</td>
<td>0.8</td>
<td>106.3</td>
<td>106.3</td>
</tr>
<tr>
<td>Before (1 μg/min)</td>
<td>2.2</td>
<td>3.8</td>
<td>43.2</td>
<td>25.0</td>
</tr>
<tr>
<td>After</td>
<td>1.0</td>
<td>1.0</td>
<td>99.0</td>
<td>77.0</td>
</tr>
<tr>
<td>Before (1 μg/min)</td>
<td>3.7</td>
<td>4.4</td>
<td>21.6</td>
<td>18.2</td>
</tr>
<tr>
<td>After</td>
<td>5.1</td>
<td>5.0</td>
<td>16.7</td>
<td>17.0</td>
</tr>
<tr>
<td>Before (2 μg/min)</td>
<td>3.1</td>
<td>18.7</td>
<td>25.8</td>
<td>4.3</td>
</tr>
<tr>
<td>After</td>
<td>6.2</td>
<td>20.6</td>
<td>12.4</td>
<td>3.7</td>
</tr>
</tbody>
</table>

TABLE 4. Effect of intra-arterial histamine on fingertip blood flow and vascular resistance before and after cimetidine

<table>
<thead>
<tr>
<th>Cimetidine (dose of histamine)</th>
<th>FBF Expected</th>
<th>FBF Observed</th>
<th>FVR Expected</th>
<th>FVR Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before (0.5 μg/min)</td>
<td>2.3</td>
<td>4.4</td>
<td>33.9</td>
<td>17.7</td>
</tr>
<tr>
<td>After</td>
<td>0.6</td>
<td>1.3</td>
<td>131.1</td>
<td>61.5</td>
</tr>
<tr>
<td>Before (0.5 μg/min)</td>
<td>3.1</td>
<td>3.9</td>
<td>28.6</td>
<td>22.3</td>
</tr>
<tr>
<td>After</td>
<td>4.0</td>
<td>5.6</td>
<td>19.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Before (0.5 μg/min)</td>
<td>1.2</td>
<td>2.5</td>
<td>62.2</td>
<td>29.6</td>
</tr>
<tr>
<td>After</td>
<td>1.0</td>
<td>0.6</td>
<td>151.9</td>
<td>127.4</td>
</tr>
<tr>
<td>Before (1 μg/min)</td>
<td>11.0</td>
<td>38.2</td>
<td>7.7</td>
<td>2.2</td>
</tr>
<tr>
<td>After</td>
<td>11.0</td>
<td>7.0</td>
<td>8.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Before (4 μg/min)</td>
<td>3.5</td>
<td>4.8</td>
<td>30.4</td>
<td>17.3</td>
</tr>
<tr>
<td>After</td>
<td>10.3</td>
<td>11.3</td>
<td>9.4</td>
<td>7.7</td>
</tr>
</tbody>
</table>

two of these three subjects did not respond to doubling the original histamine dose.

Seven subjects received 150 mg of cimetidine via the brachial artery. FBF significantly increased from $7.8 \pm 9.7$ to $16.9 \pm 21.5$ ml min$^{-1}$ 100 ml$^{-1}$ of tissue ($P = 0.047$) and FVR decreased from $28.1 \pm 27.3$ to $20.5 \pm 23.4$ units ($P < 0.047$) during the cimetidine infusions. In five subjects, histamine infusions (0.5-4 μg/min) were given before and 15 min after the cimetidine (Table 4). With histamine, the change in FBF averaged $6.5 \pm 11.6$ before and $-0.12 \pm 2.24$ ml min$^{-1}$ 100 ml$^{-1}$ of tissue after cimetidine ($P > 0.2$); FVR changes were $14.7 \pm 11.0$ and $19.1 \pm 30.3$ units respectively ($P > 0.5$). Two of the subjects showed a small or no response to histamine after cimetidine at the previous dose but responded to higher histamine doses.

Three subjects who showed a large increase in FBF with histamine infusions were restudied and both pyrilamine and cimetidine were administered. Histamine infusions were given after each of the antihistamines (Table 5). All three subjects showed an attenuated response to histamine infusions after both drugs were administered; their responses
**Histamine and fingertip circulation**

### Table 5. Effect of intra-arterial histamine on fingertip blood flow and vascular resistance after cimetidine and pyrilamine in three subjects

<table>
<thead>
<tr>
<th>Subject no. 3</th>
<th>FBF (ml⁻¹ min⁻¹ 100 ml⁻¹)</th>
<th>FVR (mmHg ml min⁻¹ 100 ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>46.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Control</td>
<td>7.1</td>
<td>15.2</td>
</tr>
<tr>
<td>H (0.5 µg/min)</td>
<td>11.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Control</td>
<td>2.9</td>
<td>36.2</td>
</tr>
<tr>
<td>Pyrilamine</td>
<td>7.2</td>
<td>14.4</td>
</tr>
<tr>
<td>Control</td>
<td>1.5</td>
<td>75.3</td>
</tr>
<tr>
<td>H (0.5 µg/min)</td>
<td>1.9</td>
<td>55.8</td>
</tr>
<tr>
<td>H (1 µg/min)</td>
<td>1.8</td>
<td>57.2</td>
</tr>
<tr>
<td>H (2 µg/min)</td>
<td>1.5</td>
<td>71.3</td>
</tr>
<tr>
<td>H (4 µg/min)</td>
<td>2.4</td>
<td>44.6</td>
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<table>
<thead>
<tr>
<th>Subject no. 12</th>
<th>FBF (ml⁻¹ min⁻¹ 100 ml⁻¹)</th>
<th>FVR (mmHg ml min⁻¹ 100 ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>5.3</td>
<td>15.1</td>
</tr>
<tr>
<td>Control</td>
<td>2.6</td>
<td>34.6</td>
</tr>
<tr>
<td>H (0.5 µg/min)</td>
<td>3.1</td>
<td>29.0</td>
</tr>
<tr>
<td>Control</td>
<td>2.0</td>
<td>45.5</td>
</tr>
<tr>
<td>Pyrilamine</td>
<td>2.9</td>
<td>29.0</td>
</tr>
<tr>
<td>Control</td>
<td>1.5</td>
<td>57.3</td>
</tr>
<tr>
<td>H (0.5 µg/min)</td>
<td>2.3</td>
<td>37.0</td>
</tr>
<tr>
<td>H (1 µg/min)</td>
<td>1.8</td>
<td>46.1</td>
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<tr>
<td>H (2 µg/min)</td>
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<td>36.1</td>
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<td>H (4 µg/min)</td>
<td>2.8</td>
<td>30.7</td>
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</table>

<table>
<thead>
<tr>
<th>Subject no. 4</th>
<th>FBF (ml⁻¹ min⁻¹ 100 ml⁻¹)</th>
<th>FVR (mmHg ml min⁻¹ 100 ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Pyrilamine</td>
<td>17.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Control</td>
<td>1.3</td>
<td>10.0</td>
</tr>
<tr>
<td>H (0.5 µg/min)</td>
<td>11.7</td>
<td>8.1</td>
</tr>
<tr>
<td>Control</td>
<td>3.2</td>
<td>29.7</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>2.5</td>
<td>38.4</td>
</tr>
<tr>
<td>Control</td>
<td>2.6</td>
<td>36.2</td>
</tr>
<tr>
<td>H (0.5 µg/min)</td>
<td>3.1</td>
<td>30.3</td>
</tr>
<tr>
<td>H (1.0 µg/min)</td>
<td>2.0</td>
<td>48.5</td>
</tr>
</tbody>
</table>

can be compared with those during their first tests shown in Table 1 by subject number.

Four subjects received intra-arterial noradrenaline to induce vasoconstriction and then infusions of histamine were added. FBF during noradrenaline infusion was 8.9 ± 10.9 and increased to 39.0 ± 8.2 ml min⁻¹ 100 ml⁻¹ of tissue with histamine \( (P < 0.005) \); FVR decreased from 18.6 ± 11.1 to 2.3 ± 0.5 units \( (P < 0.05) \). All subjects responded to 0.5 µg of histamine/min with large increases in FBF ranging from 24 to 36 ml min⁻¹ 100 ml⁻¹ of tissue.

Only one subject did not develop redness of the forearm, often blotchy in distribution, with flushing of the hand during the histamine infusions. Weals and swelling sometimes occurred on the forearm. These manifestations limited the dose of histamine that could be given and were apparent at 0.5 µg/min in six subjects. The fingers became red in 12 subjects but this was limited to the thumb in two subjects. The forearm cutaneous reactions occurred at a lower dose than finger colour changes. When histamine was given with noradrenaline, the forearm and hand only showed a diffuse blush but no demarcated redness or weals. Five of ten subjects had less forearm and hand cutaneous manifestations after pyrilamine. Cimetidine did not prevent the development of redness or weals with histamine, but most subjects showed these signs at a higher dose compared with the infusions before the antihistamines. Two subjects developed red weals with white centres with histamine after cimetidine. Only one of the three subjects who were given both antihistamines showed a slight redness of the forearm with histamine.

Four of seven subjects had redness of the forearms or fingers during cimetidine infusions. Some subjects felt warmth in their forearm or hand but no systemic symptoms occurred. Five of ten subjects who received pyrilamine had redness of their forearm or hand during the infusion. Two subjects experienced nausea, two felt like shivering and one was lightheaded. Symptoms were warmth in the forearm in four subjects and paraesthesia in the forearm and fingers in three subjects. One of the three subjects who received both antihistamines had visual hallucinations, and one felt drowsy.
Discussion

In this study, histamine increased FBF and decreased FVR during reflex sympathetic vasoconstriction induced by body cooling. The dose of histamine used was comparable with doses previously reported to increase forearm blood flow [2, 5, 6]. The dose of histamine needed to elicit vasodilatation in the reflex vasoconstricted fingertip was variable and apparently did not depend on baseline flow. Some of this variability might have resulted from differences among subjects in delivery of histamine from the brachial artery to the fingertip vessels. When vasoconstriction was induced by intra-arterial noradrenaline, the response to histamine was at the smallest dose and the increases in flow were usually larger. We have previously shown that isoprenaline also reverses fingertip vasoconstriction induced by intra-arterial noradrenaline, but unlike histamine it has no apparent effect on fingertip vasoconstriction induced by reflex sympathetic vasoconstriction [3]. Since histamine has been shown to inhibit the release of noradrenaline during stimulation of the sympathetic nerves in dog saphenous vein and anterior tibial artery strips [7], this may be the mechanism by which histamine overcomes the reflex vasoconstriction due to body cooling. The apparent greater sensitivity to histamine during noradrenaline infusion is unexplained, however, since the activity of sympathetic nerves was presumably less in the warmer environment.

The disappearance of Na\(^{131}\)I was used to distinguish nutritional from a-v shunt flow in the fingertip [8]. Fingertip nutritional blood flow was measured by the disappearance rate of the local injection of radioisotope. The difference between total FBF measured by the plethysmograph and the nutritional flow is an estimation of the a-v shunt flow. The increase in FBF with histamine involved nutritional blood flow, for the radioisotope disappearance rates showed a significant increase. This contrasts with isoprenaline, which increased only a-v shunt flow. Other vasodilator agents have not been studied to observe their effect on fingertip nutritional blood flow. Intrarterial noradrenaline has been shown to decrease both a-v shunt and nutritional blood flow; reflex sympathetic vasoconstriction affects predominantly a-v shunt flow [8]. Histamine also likely increases a-v shunt flow, for nutritional blood flows as large as the increases in FBF which occurred during histamine infusions in some subjects have not been found in previous studies [8]. An increase in FBF occurred in two subjects with no change in the radioisotope disappearance rates, which also supports an effect on a-v shunt flow. This is of interest since one of the first observations attributed to intravenous histamine was a flushing of the blush areas of the face where a-v shunts are also present [9].

Neither a histamine H\(_1\) selective antagonist, pyrilamine, nor a H\(_2\) selective antagonist, cimetidine, consistently blocked the effect of histamine on FBF. Large doses of the antihistamines were administered and responses to histamine were tested while the drugs were still active [5]. A combination of both antagonists did attenuate the response in three subjects. Duff & Whelan [5] found that the increase in forearm blood flow caused by small doses of histamine (1 \(\mu g/min\)) could be blocked by tripefanamine but pyrilamine (mepyramine) was less effective; the response to larger doses of histamine could only be reduced. Chipman & Glover [6] reported that the response of forearm blood flow of histamine which persists after pyrilamine can be abolished by a combination of pyrilamine and histamine H\(_2\) selective blockade with metiamide. In agreement with our findings, studies on hindlimb skeletal muscle or whole limb preparations in dogs also show that both histamine H\(_1\) and H\(_2\) receptor antagonism is needed to block the response of the peripheral circulation to histamine [10].

Pyrilamine did not affect the fingertip circulation whereas cimetidine significantly increased FBF and decreased FVR during the infusion. Duff & Whelan [5] reported a twofold increase in forearm blood flow during pyrilamine infusion in three subjects at the same dose over the same period of time as in our experiments. The reason for this difference is not clear, except that different vascular beds were studied. Large doses of cimetidine have been shown to vasodilate the hindlimb of the dog [11]. Since the vasodilatation produced by cimetidine is not antagonized by diphenhydramine [11, 12], it is probably not due to histamine release.

The skin manifestations of demarcated redness and weals with intra-arterial histamine prevented us from obtaining responses to graded doses. Except for flushing of the skin, these signs have not been mentioned in the forearm and hand blood flow studies on human subjects. It is possible that the plethysmographs and cuffs may have hidden them in the former studies since the same or lower doses were used in our studies. The partial suppression of the cutaneous reactions by histamine H\(_1\) or H\(_2\) receptor antagonists, the greater effect of a combination of antagonists, and the development of white centres of the weals after cimetidine have been reported by previous investigators [13-15]. The demarcated redness, weals and swelling caused by histamine were not
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seen during noradrenaline-induced vasoconstriction. This preventive effect could be due to α- or β-adrenergic actions of the infused catecholamine.

In this study we have been able to show that histamine increases FBF and decreases FVR during reflex sympathetic vasoconstriction and vasoconstriction induced by intra-arterial noradrenaline. It can increase both nutritional and a-v shunt flow. Similarly to other peripheral vascular beds, no histamine receptor subtype selectivity could be demonstrated. Since we have found reflex sympathetic fingertip vasoconstriction difficult to overcome, histamine-like drugs may prove valuable in the treatment of vasoconstrictive disease states.

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References