Role of \( \alpha \)-adrenoceptors in the maintenance of core temperature in humans

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INTRODUCTION

The thermoregulatory effects of \( \alpha \)-adrenoceptor antagonists have been previously described in animals. In rats given phentolamine, Kent and Satinoff [1] and Kent et al. [2] have shown a decrease in core temperature resulting primarily from vasodilatation and increased heat loss, which appear to be related to the peripheral rather than the central actions of the drug. Lin et al. [3], in a similar study with a rat model, also observed a decrease in core temperature. These investigators, however, reported that phentolamine induces hypothermia not only by increasing heat loss, but also by decreasing metabolic heat production, both of which appear to result from a central action of the drug. Interestingly, in a primate model in which squirrel monkeys were given doses of phentolamine similar to those given in the rat studies, there were no significant changes in core temperature despite evidence of \( \alpha \)-adrenoceptor blockade by haemodynamic indices [4].

Despite the demonstration of phentolamine-induced hypothermia in animals, the effects of \( \alpha \)-adrenoceptor antagonists on body temperature in humans are not well understood. Given the widespread clinical use of \( \alpha \)-antagonists as antihypertensives, it is important to determine whether this class of drugs significantly influences thermal balance. Hypothermia (core = 34.5°C) has been described in a case report of one individual taking typical doses of prazosin for the treatment of hypertension [5]. In a series of young, anaesthetized women undergoing minor surgical procedures, there were no differences in core temperature in those randomized to receive an intermediate dose of phentolamine and those receiving a saline control [6]. No prospective studies, however, have assessed the effects of \( \alpha \)-antagonists on body temperature in unanaesthetized humans.

We designed the current study to determine the effects of \( \alpha \)-adrenoceptor blockade on changes in core and skin-surface temperatures, vasomotor tone and metabolic heat production in human volunteers. In this study, we assessed the dose–response and

Key words: \( \alpha \)-adrenoceptor, antagonist, gender, haemodynamic, hypothermia, metabolism, phentolamine, thermoregulation.

Abbreviation: 5-HT, 5-hydroxytryptamine.

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gender-dependent effects of phentolamine on these measured outcomes. We tested the hypothesis that phentolamine decreases core temperature in a dose-dependent fashion, and that this effect results from redistribution of heat from the core to the periphery, not from a decrease in metabolic heat production.

METHODS

Subjects

After obtaining approval from the Committee on Clinical Investigation and written informed consent, five male and five female volunteers were studied. All volunteers denied having cardiovascular, endocrine or infectious diseases. All females were carefully screened to ensure that they were studied during the follicular phase of their menstrual cycle (between days 2 and 10 of the cycle). All studies were performed between 08.00 and 11.00 hours. Each subject was studied on three separate days, and on each day received a randomly assigned dose of intravenous phentolamine: 0.25 mg/kg, 0.5 mg/kg or 1.0 mg/kg.

Experimental protocol

The subjects were allowed to rest in the supine position throughout the studies. An estimation of percentage body fat was obtained using the infrared interactance technique (Futrex 1000; Futrex, Hagerstown, MD, U.S.A.) [7]. A 20-gauge intravenous catheter was inserted into the right antecubital vein with local anaesthesia. Core temperature was monitored with tympanic membrane thermocouple probes (Mon-a-therm; Mallinckrodt Medical, St Louis, MO, U.S.A.). One probe was placed in the left ear, and one in the right ear. The ear with the consistently higher temperature measurement was used to indicate core temperature to control for the possibility of inadequate insertion. Skin-surface temperature was monitored with thermocouples (Mon-a-therm) at 10 sites and a weighted average was used to calculate mean skin-surface temperature as previously described [8]: head = 6%, upper arms = 9%, forearms = 6%, hands = 4.5%, back = 19%, chest = 9.5%, abdomen = 9.5%, thigh = 19%, calves = 11.5%, and feet = 6%. All temperature data were measured by a calibrated multi-channel electronic thermometer (Iso-thermex, Columbus Instruments, Columbus, OH, U.S.A.) linked to a laptop computer and recorded onto a hard disk. This device has an accuracy of 0.1°C and precision of 0.01°C.

Peripheral perfusion was monitored in the left hand by two methods: laser Doppler flowmetry and the forearm minus fingertip skin-surface temperature gradient. Laser Doppler is a non-invasive technique used to measure capillary blood flow based on the principle of the Doppler shift of laser light, back-scattered by moving blood cells. Laser Doppler flow (Perimed-PF4, Stockholm, Sweden) was monitored in the distal middle finger using a sampling interval of 0.2 Hz. The laser Doppler probe was attached to the opposite side of the nailbed with a double-sided adhesive disc. Laser Doppler data were recorded onto a hard disk and then averaged over 1-min periods. Blood flow data are reported in laser Doppler perfusion units. Zero perfusion units corresponds to an output voltage of 0 V, while 100 perfusion units corresponds to an output voltage of 1 V.

The forearm minus fingertip skin-surface temperature gradient was also used as an index of vaso-motor tone. This method has been shown to correlate with blood flow as measured by volume plethysmography [9] and by laser Doppler flowmetry [10]. Forearm skin-surface temperature was measured over the radial aspect of the anterior surface of the left arm, half-way between the elbow and the wrist. Fingertip skin-surface temperature was measured on the left index finger, opposite the nailbed. To establish a stable baseline before phentolamine administration, forced-air skin-surface warming (Warm Touch; Mallinckrodt Medical) was used to eliminate any pre-existing vasoconstriction. A whole-body warming blanket was placed over the subject's legs and trunk, leaving the arms exposed. Warming was discontinued when the skin-surface temperature gradient in the upper extremity was equal to 0°C. The phentolamine infusion was not begun until at least 15 min after warming was discontinued.

Total body oxygen consumption was measured by indirect calorimetry (Deltatrac; Sensormedics, Anaheim, CA, U.S.A.) as an index of metabolic heat production [11]. This equipment was calibrated using a standard gas mixture before each study. A clear plastic canopy was placed over the subject's head, and measurements were obtained every minute throughout the study. Oxygen consumption data are reported as ml/min. Oxygen consumption data were unavailable for two of the five females.

After all monitors were in place, and baseline data were collected for 20 min, phentolamine was administered intravenously over a 15-min period, diluted in 100 ml of normal saline. Heart rate and arterial blood pressure were measured at 5-min intervals during the study. Heart rate was assessed by electrocardiogram, and blood pressure (systolic and diastolic) was measured in the right arm by the oscillometric technique (Marquette Tramscope, Milwaukee, WI, U.S.A.).

Data analysis

The physical characteristics of the subjects were compared by unpaired Students t-tests. All variables measured over time were analysed at 5-min intervals. Temperature, laser Doppler, blood pressure, heart rate and oxygen consumption data were com-
TABLE 1. Morphometric characteristics. *Measured by infrared inter-
stepance [7].

<table>
<thead>
<tr>
<th>Volunteer</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body fat (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>19</td>
<td>178</td>
<td>64</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>26</td>
<td>178</td>
<td>75</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>21</td>
<td>168</td>
<td>59</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>30</td>
<td>175</td>
<td>70</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>27</td>
<td>183</td>
<td>85</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>24</td>
<td>167</td>
<td>59</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>25</td>
<td>160</td>
<td>55</td>
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<td>8</td>
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<tr>
<td>9</td>
<td>Female</td>
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<tr>
<td>10</td>
<td>Female</td>
<td>24</td>
<td>163</td>
<td>60</td>
<td>19</td>
</tr>
</tbody>
</table>

pared between the low, medium and high doses by analysis of variance for repeated measures with the Bonferroni correction. To adjust for baseline differences, temperature and laser Doppler data were analysed as the change from baseline (Δ°C) with baseline defined as the average of four pre-phentolamine data points measured at 5-min intervals. In order to demonstrate gender differences, absolute values for temperature and laser Doppler data are also reported since baseline core temperature was higher in the females. Gender comparisons were done using data pooled from the three doses. Total body oxygen consumption data were also analysed as absolute values. Data are presented as means ± SEM, and P<0.05 was used to define significance.

RESULTS

Table 1 shows the physical characteristics of the subjects. Mean age was similar in the male (25±2 years) and female (26±2 years) subjects (P=0.56). Mean body weight was 71±3 kg in the male and 65±3 kg in the female subjects (P=0.14). Mean percentage body fat was 15±3 in the male and 20±3 in the female subjects (P=0.13). Mean ambient temperature was similar on the low-, medium- and high-dose days (23.4±0.5°C, 23.7±0.5°C and 23.9±0.5°C) respectively (P=0.71).

At the completion of the phentolamine infusion (15 min time point, Fig. 1) the decrease in core temperature was more significant with high-dose (0.3±0.1°C, P=0.03) and with medium-dose (0.2±0.0°C, P=0.05) phentolamine than with low-dose phentolamine (0.1±0.0°C). The maximum decrease in core temperature during the study was 0.6±0.1°C, 0.3±0.1°C, and 0.3±0.1°C with the high, medium and low doses of phentolamine respectively (Fig. 1). The maximum decrease in core temperature was greater with the high dose than with medium (P=0.04) or low (P=0.005) doses. The decrease in core temperature was not significantly different between the low and medium doses (P=0.13). Core temperature continued to decrease for 25 min, 20 min and 40 min with the low, medium and high doses, respectively, after the infusion was completed. Mean skin temperature increased above baseline with all doses (P<0.05), but was significantly different between doses (Fig. 1). Fingertip capillary blood flow measured by laser Doppler flowmetry increased significantly with medium and high doses (P=0.02 and P=0.004 respectively), relative to the low dose. The increase in blood flow was similar with medium and high doses. Blood flow remained near baseline with the low dose.

Total body oxygen consumption was similar at baseline and remained similar throughout the study (P=0.97) with the low, medium and high doses (Fig. 2). No changes from baseline were measured with either dose.

Heart rate and arterial blood pressure are shown over the course of the study in Fig. 3. Although heart rate increased significantly above the pre-phentolamine baseline with all doses (P<0.05), the
Fig. 2. Total body oxygen consumption in subjects given phentolamine. No significant changes in oxygen consumption were measured during or after the phentolamine infusion, indicating that phentolamine-induced hypothermia did not result from a decrease in metabolic heat production. △, 1.0 mg/kg; ■, 0.5 mg/kg; ○, 0.25 mg/kg.

Fig. 3. Heart rate and arterial blood pressure in subjects given phentolamine. Heart rate increased significantly above baseline with all doses, but did not differ significantly between the three doses. Neither systolic nor diastolic blood pressure changed significantly with either dose. △, 1.0 mg/kg; ■, 0.5 mg/kg; ○, 0.25 mg/kg.

difference between doses was not significant (P = 0.10). Systolic arterial blood pressure did not change significantly from baseline with any dose, and did not differ between doses (P = 0.92). Diastolic arterial blood pressure did not change significantly from baseline with any dose, and did not differ between doses (P = 0.29).

Mean core temperature was higher in females (36.9 ± 0.1°C) than in males (36.7 ± 0.1°C) at baseline (P = 0.009) and remained significantly higher during and after phentolamine (Fig. 4). However, the changes from baseline for core temperature, mean skin temperature and fingertip blood flow were similar for males and females after phentolamine administration (Fig. 5).

DISCUSSION

The results indicate that α-adrenoceptor blockade induces a dose-dependent decrease in core tempera-
ture and increase in skin temperature, with no change in metabolic heat production. These changes were not gender specific, as the average change in core temperature was similar in males and females despite a higher baseline core temperature in females. Our findings suggest that, under baseline resting conditions, \( \alpha \)-adrenoceptor 'tone' contributes to the maintenance of core temperature by constraining heat to the core thermal compartment, and \( \alpha \)-antagonists induce hypothermia by redistribution of heat from the core to the periphery. Although phentolamine has been shown to induce hypothermia in animals by increasing heat loss [1,2] as well as by decreasing metabolic heat production [3], no previous study has assessed these parameters in humans.

Walsh et al. [6], in a series of 20 patients undergoing minor surgical procedures, compared 10 patients given phentolamine with 10 patients given a saline control. The drug or saline was given as a continuous infusion during anaesthesia and surgery. Although the primary measured outcome was the glycaemic response, which was reduced as a result of higher insulin concentrations, body temperature was also measured. Core temperature measured at the tympanic membrane was similar in both groups throughout the perioperative period, and reduced below the preoperative baseline by 0.6-0.8°C. The primary confounding variable in this study was the general anaesthetic. The anaesthetic drugs included halothane and nitrous oxide, both of which have been shown to inhibit the thermoregulatory response [12-14]. General anaesthetics induce core hypothermia by redistribution of heat from the core to the periphery [15]. This redistribution most likely results from anaesthetic-induced systemic vasodilatation, a physiological response similar to that induced by phentolamine. Thus, the effects of phentolamine may have been masked by the anaesthetic drugs.

Studies in the rat model have previously demonstrated phentolamine-induced core hypothermia. Kent et al. [2] measured a decrease in core temperature after intraperitoneal administration of the drug, but not after intraventricular injection. The degree of hypothermia was dependent on ambient temperature, but even at the lowest ambient temperature (3°C) hypothermia was not induced by intraventricular administration. These investigators concluded that phentolamine-induced hypothermia was related primarily to the peripheral action of the drug, which increased heat loss via the skin, but had little or no effect on heat production. Our findings support a similar mechanism for phentolamine-induced hypothermia in humans.

Lin et al. [3], in a similar study of the thermoregulatory effects of phentolamine in rats, also demonstrated a dose-dependent and ambient temperature-dependent fall in core temperature. In contradiction to the study by Kent et al. [2], these authors concluded that hypothermia resulted primarily from the central and not the peripheral effects of the drug, and that a decrease in metabolic heat production contributed to the development of hypothermia. Since we were unable to deliver the drug centrally in our human subjects, we could not differentiate between the central and peripheral effects. However, our findings were more in agreement with those of Kent et al. [2] in that metabolic heat production was unchanged.

In contrast to the studies in rats, phentolamine was found to have no significant effect on core temperature in a primate model, in which the dose-response was assessed in conscious squirrel monkeys [4]. Despite a wide range of doses that were large enough to induce a 60% increase in heart rate and a 50% decrease in blood pressure, core temperature was unchanged. These results may be explained by the rectal temperature measurement, which may not have reflected acute changes in core temperature.

Although in the current study we have demonstrated core hypothermia induced by \( \alpha \)-adrenoceptor blockade under resting conditions, previous studies have clearly shown the role of adrenergically mediated vasoconstriction in maintaining core temperature during cold challenges. It has been known for several decades that when core temperature decreases there is a hypothalamically-mediated increase in vasomotor tone that occurs before the onset of shivering, which results in reduced cutaneous heat loss [15-18]. We have recently demonstrated that thermoregulatory vasoconstriction is mediated by increased circulating concentrations of noradrenaline, a potent \( \alpha \)-adrenoceptor agonist that increases two- to five-fold with small decreases in core temperature (0.5-1.5°C) [19,20]. In addition, we have also shown that vasoconstriction in response to the cold pressor test is attenuated by the \( \alpha \)-adrenoceptor antagonist phentolamine [10]. Thus, the findings in the current study are consistent with those of previous studies in which various models of cold stress have been shown to trigger \( \alpha \)-adrenoceptor-mediated vasoconstriction. Now we have shown that the converse is true — when vasomotor tone is reduced by \( \alpha \)-adrenoceptor blockade, core temperature decreases.

In the current study, several characteristics of the dose-response should be recognized. The maximum degree of hypothermia that developed with low and medium doses of phentolamine was similar, with temperature in both dose groups decreasing approximately 0.3°C below baseline. Core temperature decreased more significantly with the high dose to 0.5-0.6°C below baseline. Although the dose-response patterns for mean skin and core temperature were somewhat similar, capillary blood flow in the fingertip as assessed by laser Doppler flowmetry followed a different pattern. The low dose had no effect on blood flow, whereas the medium and high doses caused a similar increase in flow (approximately 60%). This shift in the dose-response curve indicates that fingertip capillary flow showed greater
sensitivity to the drug than did core and skin-surface temperatures. Although changes in blood pressure were minimal at all doses, the heart rate followed a pattern similar to core and skin-surface temperature. The failure to induce hypotension even with high-dose phentolamine probably reflects a significant increase in cardiac output which supports the arterial blood pressure in the face of decreased systemic vascular resistance.

One limitation in the current study is the non-specific nature of phentolamine as an α-adrenoceptor antagonist, since the drug blocks both α_1- and α_2-adrenoceptors. Our results do not identify which subtype of the α-adrenoceptor is specifically implicated in thermoregulatory control, and further studies will need to examine the effects of antagonists specific to adrenergic receptor subtypes. In addition, we did not study the thermoregulatory effects of non-α-blocking vasodilators to determine whether vasodilatation in the absence of α-blockade is associated with a decrease in core temperature. Although the effects of vasodilatation on core temperature have not been well studied, nifedipine has been given to humans in moderate doses with no effect on core temperature [21]. Although further studies are needed, this finding supports our conclusion that α-adrenoceptor activity is important in the maintenance of core temperature.

Although phentolamine is considered to be primarily an α-adrenoceptor antagonist, there is evidence to suggest some degree of 5-HT inhibition as well. Animal studies have shown inconsistent results regarding 5-HT and temperature regulation. When the drug is injected intraventricularly, there is some evidence for a hyperthermic effect at low doses [22, 23], but the typical response at medium and high doses is a fall in core temperature [22, 24-26].

Thus, the primary effect of 5-HT inhibition should have been an increase in core temperature. Since this did not occur, the results suggest that the hypothermic effect was primarily related to α-adrenoceptor antagonism. The peripheral vascular response in the current study also suggests that 5-HT inhibition was minimal. Since the predominant effect of 5-HT on the vasculature is vasodilatory [27], 5-HT inhibition would be expected to cause vasoconstriction, which was the opposite of what was observed.

In conclusion, we have demonstrated a dose-dependent decrease in core temperature in human subjects given phentolamine. This fall in core temperature most likely results from the redistribution of heat from the core to the periphery, and not from decreased metabolic heat production. These findings suggest that the maintenance of normothermia under baseline conditions is dependent on α-adrenergic ‘tone’, which constrains heat to the core thermal compartment. Although we have demonstrated the effects of short-term α-blockade on body temperature, further studies are necessary to determine the effects of chronic administration (e.g. antihypertensive therapy) on the thermoregulatory response.

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