Sex Differences in Peripheral Vascular Adrenergic Receptors

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Although the incidence of many vascular diseases differs in men and women, sex differences in vascular physiology have not been extensively examined in human in vivo studies. The present study compared finger blood flow responses of normal men and women with brachial artery infusions of adrenergic agonists and with other neurally and nonneurally mediated procedures. In response to phenylephrine and clonidine, men showed significant dose-related vasoconstriction while women did not. In response to isoproterenol, men showed significant dose-related vasodilation while women did not. There were no sex differences in response to intra-arterial nitroglycerin or digoxin or to reactive hyperemia, procedures that do not act through adrenergic receptors. These data show that the sensitivity and/or density of peripheral vascular adrenergic receptors is lower in women than in men. There were no sex differences in response to reflex vasoconstriction or to intra-arterial tyramine, suggesting that neurally released norepinephrine acts at \( \alpha \)-adrenergic receptors that are spatially removed from those that respond to circulating catecholamines. (Circulation Research 1987;61:581–585)

Subjects and Methods

Twenty-eight men (aged 19–33 years, mean 25.2 ± 3.2 SD) and 23 women (aged 21–33, mean 26.0 ± 3.0) gave informed consent to participate in this investigation according to procedures approved by our institutional review board. They were judged to have no evidence of any physical disorder and to be free of all medication after giving a history and completing an extensive questionnaire. All women had normal menstrual cycles and provided dates of their menses. Testing was not scheduled with regard to menstrual cycles.

Subjects were supine in a 23° C room while an 18-gauge catheter was inserted percutaneously in the brachial artery with a local anesthetic and maintained patent with 0.5 ml/min infusion of 0.9% saline solution by a Harvard 901 pump (South Natick, Mass.). The time of day of each experiment was balanced across the two groups. Finger blood flow was measured by air-displacement venous occlusion plethysmography using previously described methods and recorded 3 times per minute on a Grass 7D polygraph (Quincy, Mass.). Both hands were supported slightly above heart level. Grass oncometer cups were attached with a caulking compound to the tip of each index finger near the distal interphalangeal joint and connected by rubber tubing to Grass PT5 pressure transducers (Quincy, Mass.). These were calibrated at the beginning and end of each session by introducing known volumes of air with precision pistons attached to the transducers. All recordings were scored by one of two technicians and checked by the other. Their inter-rater reliability was 0.95, based on a sample of 100 occlusions. Heart rate and blood pressure were recorded every 4 minutes and during each drug dose with an Ohio Medical Products...
Baseline measurements were recorded for 20 minutes, after which 2 or 3 of the following compounds were infused through the catheter with additional Harvard 901 pumps: phenylephrine hydrochloride 0.125, 0.25, 0.5, 1.0, 2.0 μg/min (Winthrop-Breon, New York); clonidine hydrochloride 0.2, 0.4, 1.0, 2.0, 4.0 μg/min (Boehringer-Ingleheim, Ridgefield, Conn.); isoproterenol hydrochloride 0.025, 0.05, 0.1 μg/min (Winthrop-Breon); tyramine hydrochloride 50, 100, 200 μg/min (Regis Chemical, Morton Grove, Ill.); nitroglycerin 0.5, 1.0, 2.5, 5.0, 10.0 μg/min (Marion, Kansas City, Mo.); and digoxin 20.0 μg/min (Burroughs-Wellcome, Research Triangle Park, N.C.). Each dose was infused for 3 minutes except digoxin, which was given in one 4-minute dose. Five to ten minutes intervened between the infusion of each compound, during which blood flow in the infused hand was permitted to return to baseline. Clonidine and digoxin were always given at the end of a series since they required longer recovery times. The number of subjects receiving each compound is given in the legends to figures.

Finger blood flow measurements were averaged for the last 4 minutes of each baseline period and for each drug dose. To control for spontaneous fluctuations in finger blood flow, Duff's method was used, in which the percentage changes from the preceding baseline period were computed for each drug dose, correcting the changes in the infused hand by those occurring in the noninfused hand.

On a separate day, subjects had finger blood flow measured every 15 seconds during a 5-minute baseline period followed by a 3-minute period in which a 2.5-cm² thermoelectric stimulus applied to the back of the neck was rapidly cooled to 0°C. On a third day, subjects again had finger blood flow measured during a 5-minute baseline period and for 3-minute periods following 2-minute, 4-minute, and 8-minute periods in which finger blood flow was occluded with a 2-cm wide rubber cuff inflated to 200 mm Hg on the middle phalanx. All data were analyzed with repeated-measures analyses of variance and Newman-Keuls post hoc tests, using 0.05 as the minimum level of statistical significance.

Results

During the baseline periods, finger blood flow in the men and women and in the infused and noninfused hands did not differ significantly. Flows during baseline periods between drugs did not differ significantly from those in the preceding baseline period. During the infusion of phenylephrine, significant declines in finger blood flow in the infused hand were found in the men (p<0.05); this vasoconstriction increased with each successive dose (Figure 1). In contrast, finger blood flow in the women did not change significantly at any dose. The responses of the men were significantly different from those of the women (p<0.0005). Similarly, during the infusion of clonidine, significant dose-related vasoconstriction occurred in the men (p<0.0001) but not in the women (Figure 2). The responses of the men differed significantly from those of the women (p = 0.012). During the infusion of isoproterenol, significant increases in finger blood flow in the infused hand were found in men (p<0.05); this vasodilation increased with each dose (Figure 3). Again, blood flow in the women did not change significantly. The responses of the men were significantly different from those of the women (p<0.006).

Nitroglycerin produced significant, dose-related vasodilation (p = 0.0002) that was not significantly different (p = 0.96) in the men and women (Figure 4). Similarly, reactive hyperemia produced significant (p<0.0001) vasodilation with no significant (p = 0.84) sex difference (Figure 5). Digoxin produced significant vasoconstriction (p<0.05) that did not differ significantly (p = 0.79) in the men and women (Figure 6). Rapid cooling of the neck produced significant vasoconstriction (p<0.05) with no significant (p = 0.95) sex difference (Figure 7). Intra-arterial infusion of tyramine produced significant, dose-related vasoconstriction (p<0.003) with no significant differences (p = 0.73) between men and women (Figure 8).

There were no significant sex differences in systolic, diastolic, or mean arterial blood pressures and no
significant changes at any dose of any drug. Average resting blood pressures in the men were 128.5 mm Hg ± 9.2 SD systolic, 66.0 ± 9.8 diastolic, 84.9 ± 8.7 mean arterial pressure. For women, these values were 122.5 ± 12.4, 68.3 ± 9.1, and 82.7 ± 11.5, respectively. A small but significant decrease in heart rate (mean = 3.63 beats/min) occurred between baseline and the 1.0 μg/min phenylephrine dose. Resting heart rates were not significantly different in the men (mean 71.9 beats/min ± 9.2) and women (72.5 ± 12.3). A small but significant increase in heart rate (mean 3.42 beats/min) occurred between baseline and the 0.5 μg/min isoproterenol dose; again, there was no sex difference.

Discussion

Intra-arterial infusions of α- and β-adrenergic agonists produced dose-related finger vasoconstriction and vasodilation, respectively, in men but not in women. These findings cannot be explained by systemic changes in blood pressure or heart rate, which showed no sex differences. Moreover, the effects of such changes would be controlled for by our method of data analysis since they would be expected to affect both hands equally. Since there were no sex differences in responses to agents acting directly on blood vessels (nitroglycerin, digoxin, reactive hyperemia), the most likely interpretation of these data is that the sensitivity and/or density of peripheral vascular α- and β-adrenergic receptors is lower in women than in men. Our results are supported by those of Duff 11 who found smaller hand blood flow responses to brachial artery infusions of epinephrine in 8 of 9 normal women compared with normal men. It is not known whether these findings extend to other vascular beds as well.

Cutaneous vasodilatory responses to intra-arterial isoproterenol have varied in previous studies. Although Cobbold et al 3 observed only slight increases in hand blood flow during this procedure, Fox et al 4 found increased hand blood flow in all but one of the subjects studied. Cohen and Coffman 5 reduced blood flow with intra-arterial norepinephrine to find isoproterenol-induced digital vasodilation. In the present study, the significant β-adrenergic vasodilation in men without intra-arterial norepinephrine might be explained by lower resting baseline blood flows in our subjects. Sex differences were not examined in the previous studies.

FIGURE 3. Responses to isoproterenol in 10 men and 9 women.

FIGURE 4. Responses to nitroglycerin in 8 men and 9 women.

FIGURE 5. Peak finger blood flow responses to 2 minutes, 4 minutes, and 8 minutes vascular occlusion in 9 men and 8 women.

FIGURE 6. Responses to digoxin in 6 men and 6 women.
Responses to reflex cooling in 8 men and 8 women calculated as the percentage change from baseline to the lowest measurement during cooling.

Although men and women differed in their responses to exogenously administered adrenergic agonists, they reacted similarly to neurally mediated vasoconstricting stimuli. Reflex cooling and tyramine cause vasoconstriction through the interaction of neurally released norepinephrine with postjunctional \( \alpha \)-adrenergic receptors. Our findings suggest that neurally released norepinephrine may act at \( \alpha \)-adrenergic receptors that are spatially removed from those that respond to circulating vasoactive substances. This hypothesis has been suggested previously\(^{10-15}\) and has received some experimental support.\(^{16}\)

Desensitization of vascular adrenoceptors in women could be caused by sex hormones since von Eiff et al\(^{7}\)11 found that elevations in estrogenic activity due to the menstrual cycle or to pharmacologic administration reduced the pressor response to mental stress. However, most animal studies have found that acute and chronic administration of natural and synthetic estrogens increased vascular responses to adrenergic agonists.\(^{18,23}\)

The effects of estrogens on platelet adrenergic receptors have been studied in humans with conflicting results. Some investigations have found significant changes in platelet \( \alpha \)-adrenergic receptor binding during the menstrual cycle\(^{20,22}\) and decreased binding in men compared with women,\(^{22,24}\) whereas others have not.\(^{2,24}\)

The effects of estrogens and other sex hormones on human vascular adrenergic receptors have not, to our knowledge, been studied in vivo. This avenue of work warrants further investigation as do other possible explanations of our findings and their implications.

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