Effect of gender on endothelium-dependent dilation to bradykinin in human adipose microvessels

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EPIDEMIOLOGICAL STUDIES show that cardiovascular disease is less prevalent in premenopausal women (Pre-W) than that in age-matched men and that cardiovascular events occur more often in postmenopausal women (Post-W) (6, 11, 29). One proposed mechanism by which gender and climacteric status affect cardiovascular risk is through differences in endothelial function. In this regard, numerous studies have shown gender differences in endothelium-dependent vasodilation not only in animals (8, 12, 31) but also in humans (20). Oophorectomized animals also show diminished endothelium-dependent vasodilation (5, 19, 30). This endothelial dysfunction may contribute to the gender and climacteric differences in cardiac event rates.

A major mechanism by which estrogen modulates endothelial function is through the release of nitric oxide (NO) (5, 7, 8) and altered expression of endothelial NO synthase (NOS) protein (9, 19). Non-NO-mediated dilation is also affected by estrogen (5, 15, 26). Thus it is possible that estrogen status is responsible for the difference in endothelial function between genders and climacteric state. Previous studies to assess these questions have been performed in animals or in vivo and therefore may have been confounded by neurohumoral and metabolic influences. To determine the effect of gender and climacteric status directly on vascular reactivity in humans and to examine the mechanism of dilation, we used an isolated cannulated microvessel preparation.

The location of adipose tissue may relate to cardiovascular risk. It is known that excess storage of lipid in visceral compared with subcutaneous adipose is more strongly associated with cardiovascular risk factors such as the metabolic changes of hyperlipidemia and glucose intolerance (32). Because microvessels regulate perfusion to these tissues, we hypothesized that 1) the mechanism of arteriolar dilation to bradykinin (BK) is different in fat from the two different sites and 2) gender and climacteric state influence this dilation.

METHODS

Tissue acquisition and general protocol. Otherwise discarded human omental or subcutaneous fat was obtained at...
the time of abdominal surgery and placed in cold 4°C HEPES buffer solution. Tissues were grouped according to gender and climacteric status into one of four categories: Pre-W, Post-W, and men aged <50 yr old (Y-M) and ≥50 yr of age (O-M). Arterioles were cleaned of fat and connective tissue and were prepared for continuous measurements of diameter as described previously (17). Briefly, in a 20-ml tissue chamber, both ends of the arteriole were secured to impedance-matched glass pipettes using 10-0 Ethilon monofilament nylon sutures (Ethicon). Vessels were bathed continuously with a cold bicarbonate buffer [physiological saline solution (PSS)] consisting of (in mM) 123 NaCl, 4.7 KCl, 2.5 CaCl₂, 1.2 MgSO₄, 20 NaHCO₃, 1.2 KH₂PO₄, and 11 glucose. The preparation was then transferred to the stage of an inverted microscope (magnification ×200). Attached to the microscope were a videotracer, video monitor, and a calibrated video measurement device. Internal diameter (resolution of 2 μm) was measured manually. Vessels were incubated in oxygenated PSS (21% O₂-5% CO₂-74% N₂) for 30 min at 20 mmHg of pressure and 37°C. Pressure was slowly increased to 60 mmHg by simultaneously adjusting the heights of each reservoir attached to the pipettes, followed by a 30-min incubation period.

材 smoking. Endothelin-1 (ET-1) was obtained from Peninsula Laboratories. Other chemicals were obtained from Sigma. ET-1 was prepared in saline with 1% bovine serum albumin. Indomethacin (Indo) was prepared in 0.2 M Na₂HCO₃. Other agents were prepared in distilled water. All concentrations represent the final steady-state concentrations in the bath.

**Experimental protocols.** All pharmacological agents were added to the external bathing solution. After a 30-min equilibration period at 60 mmHg, vessels were constricted with 50 mM KCl. Vessels that did not constrict >30% were excluded (27 vessels) from analysis. Inhibitors or vehicle were added to the chamber upon warming, recording any change in diameter.

Vascular responses to increasing concentrations of BK (10⁻¹¹–10⁻⁴ M) were examined in the presence and absence of N⁶-nitro-L-arginine methyl ester (L-NAME; 10⁻⁴ M, a NOS inhibitor) and/or Indo (10⁻⁵ M, a cyclooxygenase (COX) inhibitor). Inhibitors were added to the bath 30 min before constriction with ET-1 (10⁻¹⁰–10⁻⁹ M), which was used to constrict vessels to a goal of 30–50% of their passive diameters. The volume of inhibitors was <1% of the circulating external bath solution.

In separate studies, we examined the effect of high K⁺ (30 mM)-PSS on the dilation to BK. High K⁺-PSS was prepared by substitution of KCl for NaCl on an equimolar basis. Because high K⁺-PSS reduced baseline diameter, in these protocols less supplemental ET-1 was added to achieve the same degree of preconstriction (30–50%). The endothelium-independent dilator papaverine (10⁻⁴ M) was used to determine the maximal diameter at 60 mmHg.

In a separate study, the vascular response to increasing concentrations of sodium nitroprusside (SNP; 10⁻¹⁰–10⁻⁴ M, an endothelium-independent vasodilator) was examined.

**Statistical analysis.** All data are expressed as means ± SE. Percent dilation was calculated as the percent change from the constricted diameter to the maximal passive diameter (maximal diameter in the experiment at 60 mmHg of luminal pressure) and was generally the diameter after papaverine (10⁻⁴ M). Percent constriction was determined by calculating the percent reduction in maximal diameter after the application of ET-1. Statistical comparisons of maximal percent vasodilation and ED₅₀ (equal to −log M) values under different treatments were performed by paired or unpaired Student’s t-test. A two-factor repeated-measures ANOVA was used to compare dose-response relationships between treatment groups and comparison of Pre-W, Post-W, Y-M, and O-M. Corollary dose-specific contrasts were treated with a Bonferroni post hoc test whenever the interactions were statistically significant. Multiple stepwise regression analyses were used to detect the influence of underlying diseases, age, and gender on vasodilations at various dosages. All procedures were done using “proc reg” programs of SAS for Windows version 8.2. Statistical significance was defined as a value of P < 0.05.

**RESULTS**

A total of 41 vessels from omental and 33 from subcutaneous fat with mean internal diameters of 155 ± 7 and 144 ± 3 μm (passive diameter under 60 mmHg of pressure, P = not significant), respectively, were used.

**Effect of gender on BK-induced dilation in vessels from omental fat.** Figure 1 shows BK-induced vasodilation in microvessels of omental fat from Pre-W and Y-M. BK caused vasodilation in a dose-dependent manner. ED₅₀

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*Fig. 1. Bradykinin (BK)-induced vasodilation in the absence of inhibitors (A), with indomethacin (Indo) alone (B), and with Indo + N⁶-nitro-L-arginine methyl ester (L-NAME; C) in arterioles from omental fat. Arterioles were contracted with endothelin (ET)-1. A: concentration-response curve to BK (10⁻¹¹–10⁻⁶ M) was shifted leftward in premenopausal women (Pre-W) compared with men aged <50 yr old (Y-M). ED₅₀ was greater in Pre-W vs. Y-M. Maximum dilation was similar among groups. B: treatment with Indo did not affect concentration-response curves to BK in either group. C: treatment with Indo + L-NAME reduced BK-induced dilation in Pre-W to levels similar to those observed in Y-M. #P < 0.05 vs. Y-M. All values for ED₅₀ and maximum dilation are presented in Table 1.*
combination of Indo and L-NAME reduced the maximal dilation in either gender (Fig. 1B). These data suggest that NO but not prostacyclin

pre-W, thereby eliminating the gender difference (Fig. 2C). As with omental vessels, the Indo- and L-NAME-insensitive dilation of Pre-W and Y-M was markedly reduced by 30 mM KCl (Fig. 3, A and B, and Table 2). Effect of climacteric status on BK-induced dilation in vessels from omental and subcutaneous fat. The effect of menopause on BK-induced dilation in vessel from omental fat is shown in Fig. 4 and Table 1. Vessels from Pre-W were more sensitive than those from Post-W to BK, although maximal dilations were similar. In contrast to Pre-W, Indo or Indo + L-NAME did not affect the dilation to BK in Post-W (Fig. 4B).

There was no difference in BK-induced vasodilation between Pre-W and Post-W in microvessels from subcutaneous fat (Fig. 5 and Table 3). K\textsuperscript{+}-PSS, but neither Indo nor Indo + L-NAME, affected dilation in either group. The inhibitor-resistant dilation in Post-W was

values for Pre-W were greater than those for men of similar age, Y-M, whereas maximum dilations were similar between groups (Table 1 and Fig. 1A). Thus BK-induced dilation was greater in Pre-W than in Y-M.

To examine the mechanism of this difference, we tested the effect of Indo alone, Indo + L-NAME, and high K\textsuperscript{+}-PSS. Treatment with Indo alone did not affect dilation in either gender (Fig. 1B). However, the combination of Indo and L-NAME reduced the maximal dilation and ED\textsubscript{50} values in both sexes, but more in Pre-W, thereby eliminating the gender difference (Fig. 1C). These data suggest that NO but not prostacyclin contributes to the gender difference in the response to BK in vessels from human omentum.

The Indo and L-NAME-insensitive component of the dilation accounted for ~90% of the total dilator response. This component was markedly reduced by high K\textsuperscript{+}-PSS in all groups (Table 2).

Effect of gender on BK-induced dilation in vessels from subcutaneous fat. Figure 2 shows BK-induced vasodilation in microvessels from subcutaneous fat in Pre-W and Y-M. ED\textsubscript{50} values for Pre-W were greater than those for Y-M, whereas maximum dilations were similar between groups (Table 3). Thus, similar to omentum, BK was a more potent dilator of microvessels from subcutaneous tissue in Pre-W compared with Y-M.

Treatment with Indo did not affect dilation to BK in subcutaneous fat (Table 3 and Fig. 2B); however, in contrast to omental fat, treatment with Indo + L-NAME significantly augmented dilation to BK in subcutaneous vessels from Y-M (Table 3), thereby eliminating the gender difference (Fig. 2C). As with omental vessels, the Indo- and L-NAME-insensitive dilation of Pre-W and Y-M was markedly reduced by 30 mM KCl (Fig. 3, A and B, and Table 2).

Table 2. Effect of KCl on the dilation to BK among the four groups

<table>
<thead>
<tr>
<th>n</th>
<th>Indo + L-NAME</th>
<th>Indo + L-NAME + KCl</th>
</tr>
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<tbody>
<tr>
<td>Pre-W</td>
<td>3</td>
<td>8.7 ± 0.4</td>
</tr>
<tr>
<td>Y-M</td>
<td>3</td>
<td>7.5 ± 0.4</td>
</tr>
<tr>
<td>Post-W</td>
<td>3</td>
<td>9.3 ± 0.7</td>
</tr>
<tr>
<td>O-M</td>
<td>3</td>
<td>9.3 ± 0.7</td>
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</table>

Arterioles from subcutaneous fat tissue

<table>
<thead>
<tr>
<th>n</th>
<th>Indo + L-NAME</th>
<th>Indo + L-NAME + KCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-W</td>
<td>5</td>
<td>9.6 ± 0.5</td>
</tr>
<tr>
<td>Y-M</td>
<td>5</td>
<td>10.0 ± 0.5</td>
</tr>
<tr>
<td>Post-W</td>
<td>6</td>
<td>9.4 ± 0.2</td>
</tr>
<tr>
<td>O-M</td>
<td>3</td>
<td>9.1 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of vessels used. *P < 0.05 vs. Indo + L-NAME.
also markedly reduced by 30 mM K⁺-PSS (Fig. 3C and Table 2).

Comparison of endothelium-independent dilation and effect of disease on BK-induced vasodilation. Dilation to SNP was similar among the four gender-based groups in both omental and subcutaneous fat tissues (Table 4).

Patients demographics and diagnoses are summarized in Table 5. None of the Post-W subjects were on estrogen replacement therapy (ERT). We evaluated the influence of age, gender, climacteric status, and underlying diseases (diabetes, hypertension, hypercholesterolemia, congestive heart failure, coronary artery disease, or myocardial infarction) on vasodilation to BK and SNP in vessels from omental and subcutaneous fat. With the use of multivariable regression analysis, it was determined that BK-induced vasodilation in subcutaneous fat was reduced in men (P < 0.05) but not altered by disease. In omental fat tissue, only menopause reduced dilation to BK (P < 0.05). No factor affected SNP-induced dilation.

DISCUSSION

The key findings of this study are fourfold. First, microvessels from omental tissue in Pre-W are more sensitive to BK than Post-W or men. Second, in vessels from subcutaneous fat, BK-induced vasodilation is greater in women than in men. Third, inhibition of NOS eliminates these gender and climacteric differences. Finally, endothelium-independent responses are similar between genders in both types of tissue. Taken together, these data indicate that BK-induced dilation in peripheral microvessels from human fat tissue is predictably affected by both gender and hormonal state. Furthermore, these findings are novel in demonstrating a different mechanism of microvascular reactivity in similarly sized vessels from adipose tissue in different parts of the body.

Contribution of gender and climacteric status to BK-induced vasodilation in omental fat tissue. In the present study, we demonstrated that sensitivity to BK-induced vasodilation in microvessels from omen-

![Fig. 2. BK-induced vasodilation in the absence of inhibitors (A), with Indo alone (B), and with Indo + l-NAME (C) in arterioles from subcutaneous fat. Arterioles were contracted with ET-1. A: concentration-response curve to BK (10⁻¹¹–10⁻⁶ M) was shifted leftward in Pre-W compared with Y-M. ED₅₀ was greater in Pre-W than in Y-M, although maximal dilation was similar among groups. B: Indo did not alter the BK-induced concentration-response curves in either group. C: treatment with Indo + l-NAME augmented BK-induced dilation in Y-M but not in Pre-W, eliminating the difference between groups. #P < 0.05 vs. Y-M. All values for ED₅₀ and maximum dilation are presented in Table 3.

Table 3. Comparison of ED₅₀ and maximum dilation to BK in subcutaneous fat tissue among the four groups treated with Indo or Indo + l-NAME

<table>
<thead>
<tr>
<th></th>
<th>ED₅₀ (–log M)</th>
<th>Maximum Dilation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Indo + l-NAME</td>
</tr>
<tr>
<td>Pre-W</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.7 ± 0.2</td>
<td>10.0 ± 0.3</td>
</tr>
<tr>
<td>Y-M</td>
<td>8.5 ± 0.1</td>
<td>9.9 ± 0.5</td>
</tr>
<tr>
<td>Post-W</td>
<td>9.8 ± 0.2</td>
<td>9.8 ± 0.1</td>
</tr>
<tr>
<td>O-M</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of vessels used. *P < 0.05 vs. Pre-W control and Post-W control; †P < 0.05 vs. Pre-W Indo and Post-W Indo; ‡P < 0.05 vs. Y-M control.

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tum was greater in Pre-W than in Y-M. This is the first report of gender differences in human adipose arteriolar vasoreactivity. Our data are consistent with animal studies (8, 12, 31) and with human studies of brachial conduit (20) and resistance (4) arterial dilation in vivo. Our data also indicate a prominent effect of menopause on human peripheral microvascular reactivity. In addition, we observed an important role for NOS in this gender and climacteric difference. In omental tissue, inhibiting NOS eliminated the enhanced sensitivity to BK in Pre-W compared with men, in agreement with previous studies in the rat employing acetylcholine as the endothelium-dependent agonist (31).

Contribution of gender and climacteric status to vasodilation in subcutaneous fat. Similar to omental vessels, BK-induced dilation in subcutaneous fat was greater in Pre-W than in Y-M. However, in contrast to omental tissue, there was no significant contribution of NO to the dilation in subcutaneous vessels from women. Unexpectedly, Indo + l-NAME but not Indo alone increased dilation to BK in subcutaneous arterioles from Y-M at lower doses, eliminating the gender difference. Several potential mechanisms could explain this unexpected finding.

First, because NOS can produce superoxide under conditions of reduced cofactors or substrate (22), and because l-NAME can inhibit NOS-induced superoxide production (10, 13), we speculate that l-NAME may have inhibited the production of superoxide in Y-M, thereby reducing the inhibitory effect of superoxide on subcutaneous arteriolar dilation to BK. This is consistent with previous reports that superoxide levels are higher in the vasculature of normal male than female rats (3). The combination of generated superoxide and NO may lead to formation of peroxynitrite, a more destructive reactive species that can impair dilation (25). Second, because NO can potently inhibit cytochrome P-450 epoxygenase (2) and because this enzyme is responsible for generating a common form of endothelium-dependent hyperpolarizing factor (EDHF), epoxycostrieonic acid, we speculate that l-NAME-mediated enhancement of dilation could be due to the release of inhibition of EDHF by NO levels that are subthreshold for dilation. Third, the differential gender response may also relate to a different endothelial cell calcium sensitivity (24).

Fig. 3. Effect of high K+ (30 mM)-physiological saline solution (PSS) on BK-induced dilation of microvessels from subcutaneous fat of Y-M (A), Pre-W (B), and postmenopausal women (Post-W; C). High K+ -PSS markedly inhibited the dilation that remained after treatment with Indo + l-NAME, reducing the maximal response in all groups (P < 0.05). #P < 0.05 vs. treatment with Indo + l-NAME. All values for ED$_{50}$ and maximum dilation are presented in Table 2.

Fig. 4. BK-induced dilation in the absence of inhibitors, after Indo alone, and after treatment with Indo + l-NAME in arterioles from omental fat tissue of Pre-W (A) and Post-W (B). Data from Pre-W (Fig. 1) are reanalyzed for comparison. A: in vessels from Pre-W, BK-induced dilation was not altered by Indo alone but was significantly reduced by Indo + l-NAME. B: in contrast to Pre-W, neither Indo alone nor Indo + l-NAME affected BK-induced dilation in Post-W. #P < 0.05 vs. no treatment. All values for ED$_{50}$ and maximum dilation are presented in Table 1.

Fig. 5. BK-induced dilation in the absence of inhibitors, after Indo alone, and after treatment with Indo + l-NAME in arterioles from subcutaneous fat tissue of Pre-W (A) and Post-W (B). Data from Pre-W (Fig. 2) are reanalyzed for comparison. Neither Indo alone nor Indo + l-NAME affected BK-induced dilation both in Pre-W (A) and Post-W (B). All values for ED$_{50}$ and maximum dilation are presented in Table 3.
Clinical implications. Subcutaneous and visceral adipose tissues, although similar in their role of energy storage and fat accumulation, differ in terms of their association with cardiovascular risk. Visceral fat accumulation is more closely linked to insulin resistance and to the progression of atherosclerosis than subcutaneous fat (32). Obesity with excessive visceral fat is a significant risk for cardiovascular disease that is also influenced by gender. Pre-W (14) and Post-W with ERT (28) show lower visceral fat accumulation than age-matched men and Post-W without ERT. This gender difference may relate to different rates of lipolysis because norepinephrine-induced lipolysis is greater in men than in women (16). NO released from adipocytes may contribute to the lower rate of lipolysis (1). We speculate that if NO derived from vascular endothelium also inhibits lipolysis in visceral fat, it may prevent elevation of serum free fatty acids that are linked to insulin resistance in Pre-W. Understanding of the role of the endothelial modulation of blood flow in fat may lead to new insights on vascular responses in insulin resistance syndromes.

Study limitations. We classified women according to menopausal status but did not measure plasma estrogen levels. Therefore, we could not correlate findings with estrogen levels. Furthermore, because the exact timing of the onset of menopause was not available, we cannot rule out the possibility that some women classified as postmenopausal were actually perimenopausal or only recently postclimacteric. If this were the case, the differences we observed would only underestimate the quantitative and not affect the qualitative changes associated with menopause.

None of the enrolled women were taking hormone replacement therapy. Obtaining tissue from patients on replacement therapy may further address the role of estrogens on adipose vascular reactivity.

As demonstrated in Table 5, patients in the older groups (Post-W and O-M) were more likely to have ischemic heart disease or cardiovascular risk factors. It is also likely that they were taking more medications. Because we did not record medication regimens, this may limit the comparison between subjects based on age.

The accumulation of excess visceral fat is considered a risk factor for coronary artery disease (CAD). We did not quantify visceral fat, nor did we obtain patient weight or body mass index as an indication of obesity. However, we speculate that the different mechanism of dilation in visceral compared with subcutaneous fat arterioles may relate to the significance of visceral fat as a risk factor for CAD. In future studies, the relationship between obesity and visceral fat content and BK-induced dilation should be determined. It may be that vascular abnormalities in obese subjects impair visceral but not subcutaneous mechanisms of vasodilation.

Experiments using the COX inhibitor Indo alone indicate that prostacyclin or other vasodilator prostanoids do not contribute to BK-induced dilation of adipose arterioles. However, only a few studies were performed using the NOS inhibitor L-NAME alone; thus conclusions about the role of NO must be tempered by the fact that Indo was present in most of these experiments. Demonstrated interactions between NO and COX (27) could influence these results. However, two factors favor the involvement of an NO mechanism when Indo + L-NAME together

Table 4. Comparison of ED50 and maximum dilation to sodium nitroprusside in all groups

<table>
<thead>
<tr>
<th></th>
<th>Omental</th>
<th>Subcutaneous</th>
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<tr>
<td></td>
<td>ED50 (−log M)</td>
<td>Maximum Dilation, %</td>
</tr>
<tr>
<td>Pre-W</td>
<td>7.4 ± 0.2</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>Y-M</td>
<td>7.1 ± 0.3</td>
<td>99 ± 1</td>
</tr>
<tr>
<td>Post-W</td>
<td>8.2 ± 0.3</td>
<td>99 ± 1</td>
</tr>
<tr>
<td>O-M</td>
<td>8.0 ± 0.3</td>
<td>100 ± 0</td>
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Values are means ± SE; n = no. of vessels used.

Table 5. Demographics

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<td>1</td>
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<tr>
<td>Myocardial infarction</td>
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<td>Diabetic mellitus</td>
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<td>2</td>
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<tr>
<td>Congestive heart failure</td>
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<td>8</td>
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<td>6</td>
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</table>

Age values are means ± SE; n = number of patients (n = 74 total). CAD, coronary artery disease.
were effective. First, because Indo alone did not alter dilation to BK, products of COX metabolism are likely not involved. Second, in a limited number of studies (n = 8 vessels, data not shown) where L-NAME alone was used, the associated reduced (omentum) or enhanced (subcutaneous) dilation to BK was similar to that seen with the combination of inhibitors.

Previous studies demonstrate that the response to BK is dependent on the vascular bed studied, with activation of different receptor populations producing qualitatively different responses. In the porcine basilar artery, BK induces either contraction or relaxation through endothelial B2 receptor-mediated PGI2 or NO formation, respectively (18). On the other hand, in the porcine iliac artery, low doses of BK show NO-mediated relaxation via B2 receptors and high doses yield contraction, by combined activation of B1 and B3 receptors (21). The differential effect of BK in omental and subcutaneous tissue could derive in part from a different pattern of BK receptor activation.

In conclusion, the mechanism of dilation to BK in human adipose tissue depends on gender, climacteric status, and tissue location. Endothelium-derived NO contributes to gender and climacteric differences in BK-induced microvascular dilation from omental fat in premenopausal subjects. In microvessels from subcutaneous fat, NO also contributes to gender differences, but by a different mechanism involving reduced BK-mediated dilation in male subjects.

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