Response to Can the Study of Female Rats Help Our Understanding of Women?

We thank Campbell and agree with the opinions expressed in his letter. Observations made in animal models may not always accurately reflect responses in humans. What is clear, from our research and others, is that the responses to angiotensin II in female animal models and women are not identical to those in males, and the reasons for this are not well understood.2,3 Our recent observations suggest that there are sex differences in the regulation of arterial pressure in rats with an enhanced dilator arm of the renin-angiotensin system (RAS) in sexually mature females. Furthermore, our findings add to the evidence that the angiotensin type 2 receptor is a potential target for treatment of cardiovascular disease.3 There is, as yet, little evidence from clinical studies to support such a postulate, and we acknowledge that there are instances where experimental observations in rats do not reflect the human condition. However, pharmacodynamic manipulation of the RAS in rodents generally correlates well with analogous clinical studies. The combination of rat and human studies, basic science, and population studies provides the best opportunity for translation from the “bench” to the “bedside.”

We are not surprised that large-scale clinical trials to date have not demonstrated blood pressure differences between men and women in response to antihypertensive therapies. The subjects studied in the studies cited by Campbell1 were of an age (50 to 67 years) that would indicate that most women were postmenopausal. Based on the premise that the sex differences in the RAS are estrogen dependent, one would not expect to observe sex differences in blood pressure responses to antihypertensive therapies in such older populations. Furthermore, women have often been underrepresented in clinical trials of antihypertensive agents, thus hindering inferences regarding sex differences in outcomes.

Nevertheless, there have been reports of sex differences in the response to angiotensin II and antihypertensive treatments in humans.4 Survival rates are better for women treated with angiotensin receptor blockers compared with angiotensin-converting enzyme inhibitors.4,5 The reverse is true for men.4,5 Also, there is evidence that the angiotensin type 2 receptor plays a pronounced role in arterial pressure regulation in premenopausal women.2,6 For example, during pregnancy, when the RAS is upregulated, arterial pressure actually falls, and this is associated with an increased angiotensin type 2 receptor:angiotensin type 1 receptor ratio. Also, evidence suggests that this response is absent in pregnancy-induced hypertension.6 Therefore, in premenopausal women, the vasodilator arm of the RAS may protect against cardiovascular disease. It is possible that an inability to shift the balance of the RAS toward vasodilation may increase the risk of cardiovascular disease in women, in which case, differences in response to angiotensin II between men and women would again not be expected.

Sex differences in the regulation of arterial pressure and responses to antihypertensive treatments exist in humans and rats, and the underlying mechanisms require explanation. Our data support the hypothesis that effects of estrogen on the balance between angiotensin type 1 receptor:angiotensin type 2 receptor signaling cascades contributes to these sex differences, at least in rats. Whether these effects are also in humans is yet to be established.

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Disclosures

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