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

In Campbell’s letter to the editor, he asks whether it would be “more appropriate” to study men and women rather than experimental animals to understand the effect of one’s sex on blood pressure (BP). But why is this an either-or question? Major advances in medicine are based on the continuous exchange of basic and clinical science. Animal studies enable investigation into the pathophysiological mechanisms of hypertension, which contribute to the design of clinical studies, and results from clinical studies shape the direction of basic research by identifying clinically significant findings. The history of angiotensin-converting enzyme inhibitors illustrates this constant interplay between basic and clinical science, which begins with the discovery of renin in human urine and includes the discovery of angiotensin-converting enzyme in equine plasma and an inhibitory factor in snake venom.

The findings by Sampson et al showing that angiotensin II reduces blood pressure through an angiotensin type 2 receptor (AT2R) mechanism in female but not male rats warrants clinical studies on the AT2R in both sexes. One might think that comparing data in men and women is most given the National Institutes of Health Revitalization Act of 1993 in which President Clinton signed into law the requirement that phase III clinical trials funded by the National Institutes of Health must include women when appropriate; however, this law does not include phase I trials in which drug safety, tolerability, pharmacokinetics, and pharmacodynamics are examined or the larger phase II trials designed to test dosing and efficacy. Furthermore, there is no requirement that basic science or translational studies be conducted in both sexes. We must consider the consequences of expanding our basic science foundation primarily from studies conducted in cells, tissues, and animals of the male sex. This male-leaning tower of knowledge has already been blamed for why the risk of adverse drug events is reportedly greater in women than in men and why ≥8 of 10 drugs removed from the market by the Food and Drug Administration exhibit greater adverse effects in women than in men. If sex differences in rat AT2R activity do have clinical significance, Campbell asks, then why did clinical trials such as the Losartan Intervention for Endpoint Reduction in Hypertension Study of ~10,000 postmenopausal women and age-matched men not show sex differences in blood pressure responses to antihypertensives? But how can these negative results rule out the clinical significance of the AT3R? Many questions exist that deserve consideration. First, what role does the AT4R play in human blood pressure regulation under physiological and pathological conditions? Does this role differ between men and women? What regulates AT3R activity in humans? Are these regulatory pathways sex specific? Is the AT3R a valuable therapeutic target for treating human hypertension? Would therapeutic value be sex specific? Although I may disagree with Campbell on the extent to which experimental animal research contributes to our understanding of human hypertension, we both do agree that clinical research designed to investigate the impact of one’s sex on the causes and control of hypertension is imperative if we are to fully understand hypertension in both sexes.

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Disclosures

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