Editorial Commentary

Angiotensin Type 2 Receptor
Hidden Partner

Kate M. Denton

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The biological function of the angiotensin type 2 receptor (AT2R) has been difficult to identify, with its role to a large extent masked by the predominate actions of angiotensin II (AngII) at the AT1R. However, it is now recognized that the AT2R opposes the actions of the AT1R in the cardiovascular system. All the classical excitatory effects evoked by AngII (vasoconstriction, renal sodium retention, vascular growth, and inflammation) result from AT1R stimulation, whereas AT2R stimulation causes vasodilatation, sodium excretion, apoptosis, anti-inflammatory and antifibrotic effects. Thus, the AT2R is now identified as an important member of the protective arm of the rennin–angiotensin system that acts as an independent biological modulator of AngII–AT1R function. Accumulating evidence also suggests that the expression and function of the AT2R are sexually dimorphic, with the AT1R having an enhanced role in women.

Cardiovascular disease, incidence and course, can be markedly affected by sex chromosomal and hormonal influences. The primary sex-biasing elements are those encoded on the sex chromosomes that are inherently different in the men and women. These genes as well as downstream factors, such as gonadal hormones, act directly on tissues to produce sex differences in structure and function of tissues. In the study by Danser et al, published in this issue of Hypertension, the four core genotype model was used to delineate the contribution of sex-chromosome complement and sex hormones to AT1R-mediated vasodilation. In the four core genotype model the gonadal sex of the mouse is not related to the sex chromosome complement as the testis-determining Sry gene has been transferred to an autosome. The 4 genotypes generated are XX gonadal males or females, and XY gonadal males or females. The four core genotype model allows the examination of the influence of sex hormones (estrogen versus testosterone), and the interaction of these factors. There are limitations to the four core genotype model that should be kept in mind when interpreting studies in this model. The absence of the Sry gene from the Y-chromosome and its presence on an autosome may influence transcription of other genes in the same regions, which may contribute to the responses observed.

Danser et al demonstrated that the AT2R reduced the constrictor response to AngII in Iliac arteries in intact XX females, because in the presence of the AT2R antagonist, PD123319, the constrictor response to AngII was enhanced. This action of the AT2R to attenuate the constrictor response to AngII was absent in the XXSry males, XY females, and ovariectomized XX females, leading to the conclusion that the response required both estrogen and an XX complement. The dependence of AT2R actions on the presence of estrogen has been reported previously in other models. However, the over-riding importance of the X-chromosome for AT2R function has not been previously demonstrated. The AT2R gene is located on the X-chromosome. In general, 1 copy of the X-chromosome undergoes inactivation, although this is not always the case as some genes have a dose-dependent function in women by escaping X inactivation. It has also been suggested that inactivation or activation of genes on the X-chromosome may be epigenetically regulated and tissue-specific. Thus, the location of the AT2R on the X-chromosome suggests a greater role for the AT2R in women, and given the protective roles of the AT2R in cardiovascular disease this warrants further investigation.

The study by Danser et al clearly demonstrated that AT2R function was dependent on the sex-chromosome complement. However, an alternative to the permissive role of a XX complement is the possibility that the Y-chromosome, and in particular Sry, may play a repressive role in AT2R transcription. Recently, Araujo et al demonstrated in cell-based studies that Sry repressed the AT2R promoter, offering a potential mechanism for the lower AT2R expression observed in men. That said it was also demonstrated that SOX3, the analogous gene on the X-chromosome, also repressed the AT2R gene promoter, which would suggest that SOX3 should reduce AT2R expression in women. However, this same study demonstrated that SOX3 was only expressed in brain and testis. Therefore, Sry and SOX3 genes may differentially regulate AT2R expression and function, between the sexes. A full understanding of the regulation of components of the rennin–angiotensin system, and thus the functional balance of the different arms of the rennin–angiotensin system between the sexes, including the role of the AT2R in the protective arm of the rennin–angiotensin system, is still to be delineated and warrants further study.

There are major sex differences in the expression and function of AT1R, and studies primarily in rodents suggest an enhanced role for the regulation of renal function and arterial
pressure in young women, that disappear with age.\textsuperscript{3,7} This has led to the suggestion that targeting the AT\textsubscript{2}R may be beneficial in women with cardiovascular disease. A caveat to this conclusion is that supporting evidence available in humans is limited.\textsuperscript{8,9} Men die at a greater rate of cardiovascular-related diseases, except at the oldest ages, when compared with women. Thus, understanding how the AT\textsubscript{2}R is upregulated in women and repressed in men could be used to lower morbidity and mortality in men at all ages, and maintain protection in postmenopausal women, and this possibility should be explored further.

Disclosures

None.

References

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