Impact of the Direct Angiotensin II Type 2 Receptor Stimulation on Renal Function
Toward a Sex-Specific Therapeutic Approach for Hypertension
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Hypertension and cardiovascular diseases are more prevalent in men than in premenopausal women of the same age. However, after menopause, this cardiovascular protection in women is lost, possibly because of the unbalance of estrogen production and other sex hormones in postmenopause. Although the mechanisms underlying these sex differences remain unclear, divergences in the function of the renin-angiotensin system (RAS) and differences in the response to stimulation and inhibition of RAS in men and premenopausal women have been proposed.

RAS is involved in blood pressure regulation by modulating vascular tone and renal excretory function. In particular, the kidney is involved in the long-term regulation of arterial pressure by modulating sodium excretion.

It is now generally accepted that RAS organization is dual and that beside the well-known main pressor axis (angiotensin-converting enzyme/angiotensin [Ang] II/Ang type 1 receptor [AT1R]), there is a second depressor protective axis consisting of Ang type 2 receptor (AT2R), angiotensin-converting enzyme 2, Ang-(1–7), and MasR. In particular, AT2R mediates the vasodilatory and natriuretic actions of angiotensin peptides. AT2R is expressed throughout the kidney in both vascular and tubular elements, and it is greatly expressed in renal proximal tubule cells. AT2R induces vasodilation in both resistance and capacitance vessels, protects the kidney from AT1R-mediated inflammation and ischemic damage, and may contribute to the beneficial natriuretic response to angiotensin receptor blocker.

In humans and animal models, sex differences exist in the regulation of arterial pressure and renal function by RAS, possibly through a different balance in the pressor and depressor arms of the system. Accumulating evidence suggests that vasodepressor RAS pathways are enhanced in women and that AT2R plays a prominent role in arterial pressure regulation in premenopausal women. In normotensive and hypertensive mice and rats, AT2R expression is enhanced in the vasculature of females, particularly in the kidney. It has been shown that AT2R is expressed to a greater extent in the kidney and vascularization of female rats and mice. Therefore, AT2R seems to play a role in opposing the pressor actions induced by AT1R stimulation in females via an estrogen-dependent mechanism and may contribute to sex differences in arterial pressure control, causing vasodilation and decreased renal sodium reabsorption.

AT2R attenuates the Ang II–dependent resetting of tubuloglomerular feedback, which contributes to setting pressure-natriuresis properties. This effect is not evident in male mice and underlines the protective role of the AT2R against the prohypertensive effects of Ang II in women. Studies in normotensive rats have shown that females demonstrate a leftward shift in the pressure-natriuresis relationship such that they are able to excrete the same amount of sodium as males at lower arterial pressure levels. This may occur through the contribution of AT2-related mechanisms. Interestingly, AT2R stimulation does not increase glomerular filtration rate, possibly because of direct effects on both preglomerular and postglomerular arterioles or, alternatively, a direct relaxation of podocytes, thus reducing, in turn, the surface area available for filtration. Hence, the increased excretion of sodium in response to AT2R stimulation might be attributed to an inhibition of tubular sodium reabsorption, independent of AT2R-mediated changes in renal hemodynamics.

The study by Hilliard et al published in this issue of Hypertension further extends the knowledge on the direct AT2R stimulation with the novel nonpeptide AT2R agonist, Compound 21 (C21), on renal function, in hypertensive conditions in female rats. Acute AT2R stimulation enhanced renal vasodilatation and sodium excretion, without concomitant alterations in glomerular filtration rate in female but not in male hypertensive rats. Although these experiments were performed in denervated kidneys, the main findings of the study demonstrate a favorable effect of the direct AT2R stimulation on renal hemodynamics and natriuresis in vivo, particularly in female hypertensive rats. This suggests that the direct AT2R stimulation could represent an attractive and feasible therapeutic approach for the treatment of hypertension and associated renal disease, at least in premenopausal women.

However, it has been shown that the direct AT2R stimulation with C21 does not induce a significant effect on systemic blood pressure in both male and female rodents, while AT2R stimulation induces renal vasodilation and natriuretic effects in both normotensive male and female rats, although in a...
dose-dependent manner only in female rats. Also, in spontaneously hypertensive rats, AT2R stimulation with C21 induced renal vasodilatory and natriuretic effects in females, in the absence of any significant changes in arterial pressure. Thus, the direct AT2R stimulation seems to be involved in the modulation of renal vascular tone and natriuresis, particularly in premenopausal females. On the other hand, C21 is not directly involved in systemic blood pressure regulation, unless AT1R is previously blocked. Indeed, it has been shown that C21 promotes vasorelaxation in vitro, which in turn is associated with vasodepressor responses in conscious spontaneously hypertensive rats previously treated with the angiotensin receptor blocker candesartan. Furthermore, recent data show that the AT2R-mediated renal vasodilator effect after stimulation with C21 is unmasked by angiotensin-converting enzyme inhibition in spontaneously hypertensive rats but not in normotensive rats. This suggests that upregulation of renal vascular AT2R in hypertension is associated with a countervailing function opposing the increased AT1R-mediated tonic renal vasoconstriction. Thus, the counter-regulatory function of AT1R and AT2R may occur in the vasculature of hypertensive rodents, as described previously in humans also. This implies the need of AT1R blockade to obtain the therapeutic benefit of AT2R stimulation in the vasculature of hypertensive subjects and indirectly supports the existence of a cross-talk between Ang II receptor subtypes. Nevertheless, the sexual dimorphism in blood pressure control might affect the response of men and women to different therapeutic approaches. Because AT2R expression is regulated by estrogen, AT2R agonist therapy might represent an innovative therapeutic approach to treat hypertension in premenopausal women. However, the long-term and sex-specific responses to direct AT2R stimulation during hypertension in the presence and absence of combined AT1R blockade need further elucidation in future studies to establish the efficacy of the AT2R agonism as a therapeutic target for cardiovascular disease, particularly in women.

Furthermore, whether the favorable effect of the direct AT2R stimulation on renal function and natriuresis is still present after menopause has not been established yet, and it needs to be clarified with specific studies.

Disclosures

None.

References
