Angiotensin II Type 2 Receptor Effects: Lesson From a Human Model of Vascular Hyporeactivity. Letter Regarding Kemp et al

Angiotensin II (Ang II) regulates a broad spectrum of cardiovascular and renal processes ranging from vasoconstriction to inflammatory processes, including atherosclerosis and vascular ageing. Ang II determines most of its effects via activation of 2 G-protein–coupled receptors with opposite effects: the type 1 (AT₁R) and the type 2 receptors (AT₂R).

The relationships and interactions between AT₁R and AT₂R signals, their roles in the control of vascular tone and cardiovascular remodeling, and the underlying mechanisms are complex and remain to be defined fully.

Kemp et al. have added another relevant piece of evidence in this field through an elegant study in an animal model of AT₁R stimulation recently published in the journal. These authors have, in fact, demonstrated that AT₁R stimulation via the specific non-peptide AT₁R agonist compound-21 (C-21) increased the urinary sodium excretion without affecting the mean arterial blood pressure and the renal hemodynamics. This effect has been shown to be dependent on a bradykinin-nitric oxide-cyclic guanosine monophosphate pathway. Finally, the authors demonstrated that in a rat model of Ang II–dependent hypertension, the intrarenal monophosphate pathway. Finally, the authors demonstrated that the effect of Ang II on AT₁R serves to maintain blood pressure, whereas at high Ang II concentrations, AT₂R-mediated vasodilation comes into play. However, it seems that AT₂R effects are not dependent only on different binding affinity of Ang II for the 2 receptors, but instead are linked with an AT₁R effect, which is counteracting the Ang II hypertensive effect partially.

These results shed more light on previous speculations that the interplay of AT₁R and AT₂R is not a matter of balancing between opposite actions but rather a shift of gear, where at physiological concentration Ang II does not bind to AT₁R and at these levels the effect of Ang II on AT₁R serves to maintain blood pressure, whereas at high Ang II concentrations, AT₁R-mediated vasodilation comes into play. However, it seems that AT₂R effects are not dependent only on different binding affinity of Ang II for the 2 receptors, but instead are linked with an AT₁R effect, which is counteracting the Ang II effects via AT₁R.

We suggest that the relevance of the data provided by Kemp et al. in an animal model is supported by the results of our studies in a human model of endogenous AT₁R stimulation and blunted Ang II signaling via AT₁R, the Bartter/Gitelman (BS/GS) syndromes.

BS/GS syndromes are rare diseases caused by gene defects in specific kidney transporters and ion channels and are characterized by the activation of the renin–angiotensin–aldosterone system with high plasma levels of Ang II, and aldosterone, yet normotension or hypotension, hyporesponsiveness to pressor agents and the activation of antiatherosclerotic and antiremodeling defenses. Patients with BS/GS syndromes likely represent a human model of in vivo endogenous antagonism of Ang II signaling via AT₁R as suggested by the reduced expression of the α subunit of Gq protein, of the p63RhoGEF, and of downregulation of RhoA/Rho-kinase system, and by the upregulation of the regulator of G protein signaling-2 and of the nitric oxide system absence of cardiovascular remodeling in terms of carotid intima-media thickness and cardiac hypertrophy despite high Ang II levels. Furthermore, and particularly relevant with the study of Kemp et al., we have demonstrated that Ang II signaling via AT₁R is activated in patients with BS/GS. In particular, this study investigated the effect of Ang II on AT₁R signaling in terms of mitogen-activated protein kinase phosphatase-1 (MKP-1) expression, a main effector of AT₁R signaling, whose protein expression is associated with ERK1/2 (extracellular signal regulated kinase) activation. Ang II stimulation of BS/GS fibroblasts induced a transient phosphorylation of ERK1/2 with a decline brisker than healthy controls and a parallel increase of MKP-1 protein expression. The AT₁R inhibitor PD123319 extended the ERK1/2 phosphorylation response in BS/GS fibroblasts to the same level as the prolonged ERK1/2 phosphorylation increase found in the fibroblasts from healthy subjects. Moreover, in fibroblasts from healthy subjects incubated with the AT₁R inhibitor losartan, Ang II determined an ERK1/2 phosphorylation and MKP-1 response curve comparable with that of BS/GS. Taken together, these data confirm patients with BS/GS as a human model of blunted AT₁R signaling and prove the activation of AT₂R signaling in the presence of high Ang II levels. In addition, the Ang II effects in patients with BS/GS may provide further insight into the AT₁R and AT₂R interactions because they suggest that AT₂R-activated MKP-1 affects ERK1/2 phosphorylation, which is strongly linked to the AT₁R stimulated cardiovascular hypertrophic response.

Moreover, the in vitro demonstration that the effects of high Ang II levels on MKP-1 expression and ERK1/2 phosphorylation are blunted by the AT₁R inhibitor PD123319 in fibroblasts of patients with BS/GS and by the AT₁R inhibitor losartan plus PD123319 in healthy subjects’ fibroblasts, together with the clinical evidence in patients with BS/GS of reduced vascular tone and normotension/hypotension, despite the activation of the renin–angiotensin–aldosterone system, corroborate in a human model the findings by Kemp et al. in an animal model and strongly support with data in a human model characterized by the activation of antihypertensive, antiatherosclerotic, and antiremodeling defenses, the evidence and conclusions of Kemp et al. on the stimulation of AT₂R signaling provided in animals.

Disclosures

None.

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References


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