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 inflammatory processes, including atherosclerosis and vascular 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 AT$_2$R stimulation recently published in the journal. These authors have, in fact, demonstrated that AT$_2$R stimulation via the specific non-peptide AT$_2$R 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 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 AT$_1$R is activated in patients with BS/GS. In particular, this study investigated the effect of Ang II on AT$_1$R signaling in terms of mitogen-activated protein kinase phosphatase-1 (MKP-1) expression, a main effector of AT$_1$R 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 AT$_1$R 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 AT$_1$R 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 AT$_1$R signaling and prove the activation of AT$_1$R 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 AT$_1$R and AT$_2$R interactions because they suggest that AT$_2$R-activated MKP-1 affects ERK1/2 phosphorylation, which is strongly linked to the AT$_1$R 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 AT$_1$R inhibitor PD123319 in fibroblasts of patients with BS/GS and by the AT$_1$R 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 AT$_2$R signaling provided in animals.

None.

Disclosures

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