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 (AT\textsubscript{1}R) and the type 2 receptors (AT\textsubscript{2}R).

The relationships and interactions between AT\textsubscript{1}R and AT\textsubscript{2}R 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\textsuperscript{1} have added another relevant piece of evidence in this field through an elegant study in an animal model of AT\textsubscript{2}R stimulation recently published in the journal. These authors have, in fact, demonstrated that AT\textsubscript{2}R stimulation via the specific non-peptide AT\textsubscript{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,\textsuperscript{5} and by the upregulation of the regulator of G protein signaling-2 (RGS2)\textsuperscript{7} and of the nitric oxide system,\textsuperscript{4,7,8} the in vitro demonstration that the effects of high Ang II levels on MKP-1 expression are blunted by the AT\textsubscript{2}R inhibitor PD123319 in fibroblasts from healthy subjects incubated with the AT\textsubscript{1}R inhibitor losartan, 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\textsubscript{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\textsubscript{1}R inhibitor losartan, Ang II determined an ERK1/2 phosphorylation and MKP-1 response curve comparable with that of BS/GS.\textsuperscript{10} Taken together, these data confirm patients with BS/GS as a human model of blunted AT\textsubscript{2}R signaling and prove the activation of AT\textsubscript{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\textsubscript{1}R and AT\textsubscript{2}R interactions because they suggest that AT\textsubscript{1}R-activated MKP-1 affects ERK1/2 phosphorylation, which is strongly linked to the AT\textsubscript{1}R stimulated cardiovascular hypertrophic response.\textsuperscript{10}

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\textsubscript{1}R inhibitor PD123319 in fibroblasts of patients with BS/GS and by the AT\textsubscript{1}R inhibitor losartan plus PD123319 in healthy subjects' fibroblasts,\textsuperscript{10} 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\textsuperscript{1} in an animal model and strongly support with data in a human model characterized by the activation of antihypertensive, antiatherosclerotic, and antiremodeling defenses,\textsuperscript{3} the evidence and conclusions of Kemp et al\textsuperscript{1} on the stimulation of AT\textsubscript{2}R signaling provided in animals.

Disclosures

None.

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