

The curtain rises on the renin-angiotensin system: AT2 receptors are in the spotlight.

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Editorial

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Despite the critical role of the renin–angiotensin system as a target for cardiovascular and renal pharmacotherapy of common diseases such as hypertension, congestive heart failure, and diabetic renal insufficiency, uncertainties remain as to the essential role of key components. For example, the angiotensin II Type II (AT₂) receptor, initially described pharmacologically more than 10 years ago and cloned more recently, has remained elusive as to its precise functional significance. Of particular interest, in this regard, is the manuscript by Siragy and Carey (1) in the current issue of this journal that expands our understanding of the renal AT₂ receptor subtype, its signalling mechanism, and function.

The two major isoforms of the angiotensin receptor are the type 1 (AT₁) and the AT₂. The classification was based on pharmacological properties, cloning (~30% sequence homology), and signalling (2–4). Furthermore, the distribution of these receptors differed strikingly, suggesting little functional overlap. For example, AT₁ receptors are widely distributed and appear to mediate “all” the relevant biological effects of angiotensin II (e.g., vasoconstriction, steroid biosynthesis, ion transport, neurotransmission, mitogenesis, etc.). By contrast, AT₂ receptors are distributed widely in the fetus but localized to discrete brain nuclei and renal locations in the adult. Until recently AT₂ receptors were relegated to “unidentified roles” as modulators of fetal development and postnatal cellular function(s) (4). Surprisingly, recent observations using mice with targeted disruption of the AT₂ receptor gene demonstrate apparently normal embryogenesis and, thereby, fail to support the hypothesis of an essential role in fetal development (5, 6). Alternatively, much attention has focused on the newly described antimitogenic role of AT₂ receptors first observed in rat coronary artery endothelial cells, an opposing action to AT₁-mediated mitogenesis (7). Moreover, AT₂ receptors appear to counteract classical pressor responses to angiotensin II since basal blood pressure was increased and the pressor response to angiotensin II was enhanced in AT₂-deficient transgenic mice (5, 6). The precise mechanisms of these recent observations have not been defined.

Siragy and Carey explore the role of the renal AT₂ receptor system using a unique renal interstitial fluid microdialysis system that permits sampling in rats in the absence of hemodynamic perturbations (1). The use of specific pharmacological blockers of the AT₁ receptor (Losartan) and the AT₂ receptor (PD123319) demonstrated independent modulation of renal eicosanoid biosynthesis and guanylate cyclase, respectively. The AT₂ receptor mediated increments in cyclic guanosine 3',5'-monophosphate (cGMP), while the AT₁ receptor mediated increments in PGE₂, an effect that was potentiated fur-

ther in the presence of an AT₂ receptor blocker. Effects were observed during normal sodium balance with exogenous angiotensin II administration and after activation of the endogenous renin–angiotensin system. These observations have important implications as to the physiological role of renal AT₂ receptor and signaling linked to this receptor subtype, particularly as relates to blunting of blood pressure–induced sodium excretion, a response that also appears to be AT₂ mediated (8). Pressure–natriuresis is of extreme importance to the control of blood pressure and renal function.

Because of inherent limitations in physiological studies, a precise cellular/molecular mechanism cannot be determined for the AT₂-mediated changes in cGMP using this model. Unresolved questions of interest include the following: Is the AT₂-mediated mechanism related to particulate or soluble guanylate cyclase, the NO synthase system, or phosphotyrosine phosphatase? What is the cell type that mediates the effect (vascular, interstitial, and/or epithelial)? Given the intense interest in AT₂-mediated signaling, receptor distribution, and physiologic significance, it is important to better define this novel AT₂ receptor pathway.

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