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Angiotensin II mediates Tyr-dephosphorylation in rat fetal kidney membranes

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Abstract

Angiotensin II (Ang II) elicits a variety of physiological effects through specific Ang II receptors in numerous tissues. In addition, Ang II is a modulator of cellular growth and exerts a positive or negative effect on cell growth depending on which receptor subtype is activated. Expression of the intrarenal AT_2 receptors occurs at its highest levels in the fetal kidney, with a rapid decline after birth. In the present paper, we performed a study on the signaling mechanism of Ang II receptors in rat fetal (E20) kidney, a rich source of AT_2 receptors, where both Ang II receptor subtypes are present. Ang II induces Tyr-dephosphorylation of proteins in rat fetal kidney membranes. The response is dose-dependent, with a reduction of 20% with respect to the control (100%), signal that is completely reversed by Ang II AT_2 competitor PD123319. Orthovanadate, the inhibitor of phospho-Tyr-phosphatases (PTPase), reverts Ang II effect, suggesting the involvement of a protein tyrosine phosphatase. The peptide analog of Ang II, CGP42112, exhibits an agonist effect, which is dose-dependent. Thus, in rat fetal (E20) kidney, the Ang-induced protein Tyr-dephosphorylation of several proteins is mediated by AT_2 receptors, mechanism that involves an orthovanadate sensitive PTPase. (Mol Cell Biochem **254**: 137–143, 2003)

Key words: Ang II receptor subtypes, Tyr-dephosphorylation, signal transduction, kidney development

Introduction

Angiotensin II (Ang II) elicits a variety of physiological effects through specific Ang II receptors in numerous tissues. In addition, Ang II is a modulator of cellular growth and exerts a positive or negative effect on cell growth depending on which subtype of receptor is activated [1–3].

Ang II acts on its target tissues through binding to two main membrane receptor subtypes: AT_1 receptors, specifically blocked by losartan and AT_2 receptors, selectively displaced by CGP42112 or PD123319 [2, 3]. Both receptor subtypes belong to the superfamily of G-protein coupled receptors [4–7].

Most of Ang II functions in the cardiovascular system are mediated by AT_1 receptors, whereas little information is available regarding the physiological role of AT_2 receptors. However, recent studies on mice lacking AT_2 receptors as well as cardiac-specific overexpression of AT_2 receptors suggested the involvement of these receptors on pressure control and chronotropic control of the heart [8–10].

In the kidney, a key organ in the control of fluid homeostasis, Ang II mediates effects as arteriolar vasoconstriction, mesangial cell contraction and tubular cell hypertrophy and hyperplasia. These well-described effects occur via interaction with AT_1 receptors, present in all nephron segments [11].

The possible role of Ang II AT_2 subtype on development has been already proposed on the basis of the high expression level of these receptors early during development [3, 12–14]. The presence of AT_1 and AT_2 receptors in developmental kidney have been shown by different methods [12, 14, 15]. Expression of intrarenal AT_2 receptors occurs at its highest levels in the fetal kidney, with a rapid decline after birth. However, recent immunohistochemical studies showed AT_2 receptors in adult kidney, within glomeruli, tubules and interstitial cells [16]. Previous studies by autoradiography

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