Intracellular Angiotensin II AT1 Receptor—an Important Component of the Cardiac Intracrine Action of the Peptide

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Editorial

The systemic Renin Angiotensin System (RAS) depends on the release of renin and the action of the enzyme on angiotensinogen to generate the decapptide angiotensin I which in turn is converted to angiotensin I by the Angiotensin Converting Enzyme (ACE) in the pulmonary circulation.

Evidence is now available that there is a local RAS in the heart [1-3] and that different components of the renin angiotensin system are taken up by different tissues [4] thereby influencing the synthesis of Angiotensin II (Ang II) locally [3-5]. Several observations indicate that the local renin angiotensin system in the heart has a functional intracrine component [3,6-9]. Indeed, when angiotensin II is dialyzed into a cardiomyocyte from the failing heart, there is cellular uncoupling elicited by a drastic decline of gap junctional conductance [6,7,10].

Recently, it was found that the intracellular angiotensin II is involved in the regulation of heart excitability in the intact ventricle of the failing heart [11] by inhibiting the potassium current. Indeed, when the peptide is injected into ventricular cells of the failing heart a hyperpolarization of 7.7 ± 4.3 ± mV (n=39) (P<0.05) was found concurrently with an increase of the action potential duration and refactoriness [11]. The increase of action potential duration was inhibited by intracellular losartan which supports the view that intracellular AT1 receptors are involved in the effect of the peptide. All the effects of angiotensin II were inhibited by PKC (Protein Kinase C) inhibition [11]. Of particular interest was the finding that the effect of intracellular injection of angiotensin II remains for more than one hour after interruption of the peptide injection [11].

Previous findings indicated that intracellular AT1 receptors are involved in the effect of intracellular angiotensin II on cell communication in heart cells [12] and recently it was found that intracellular angiotensin II alters the cellular functions in kidney tubular cells [13,14]. The intracrine action of angiotensin II on inward calcium current of cardiac cells is inhibited by eplerenone—a mineralocorticoid hormone inhibitor. This effect of eplerenone was related to a decrease in membrane-bound and intracellular levels of AT1 receptors [8].

Further studies on the role of intracellular AT1 receptors have shown that microinjected Ang-II preferentially bind to nuclear sites of isolated cardiomyocytes and that cardiomyocyte nuclear membranes possess angiotensin receptors that couple to nuclear signaling pathways and regulate transcription [15].

In conclusion, evidence is available that the activation of intracellular angiotensin II AT1 receptors changes cell communication and the conductance of membrane ionic channels with consequent alteration of cardiac excitability. The regulation of transcription within the nuclear envelope elicited by intracellular angiotensin II [15] indicates that the peptide has profound effects on heart cell function and on the incidence of cardiac rhythm abnormalities.

References


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