Is angiotensin 1-7 an agonist for the AT2 receptor?

Kamphuis W, Ziegler D**, Weske M**, Ronken E*
Solvay Pharmaceuticals Research Laboratories, *Weesp, **Hannover, Germany

The Renin-Angiotensin-System (RAS) is a key regulator of blood pressure. Currently, two distinct receptors for angiotensin II have been identified and characterised; the AT1 and AT2 receptor. AT1 receptors mediate vasoconstriction upon stimulation, whereas AT2 receptors are implicated in hypotensive effects.
Processing of angiotensinogen yields a number of biologically active peptides, including angiotensin 1-8 (angiotensin II) and angiotensin 1-7. Whereas angiotensin II is the cognate ligand for AT1 and AT2, the mechanism through which angiotensin 1-7 induces its powerful hypotensive effect is yet unclear. This study aims to identify this novel subtype angiotensin receptor.
In vitro data were obtained using the cytosensor microphysiometer, which measures cellular acidification. Using a rat endothelial cell-line (RAEC), biological activity was found upon stimulation by angiotensin II (pEC_{50} 8.0 ± 0.2). The response could be counteracted completely by angiotensin 1-7 (1 µM). The effect of angiotensin 1-7 could be antagonised by its putative antagonist dAla-angiotensin 1-7 (1 µM). However, dAla-angiotensin 1-7 did not alter angiotensin II activity. The effects of angiotensin 1-7 disappeared during culturing while the angiotensin II effect was preserved, including its sensitivity to Losartan, an AT1 antagonist.
Secondly, receptor binding was performed on AT1 and AT2 receptors.
^{125}I-Angiotensin II binding could be displaced completely by angiotensin 1-7 (pKi 6.31) on the AT1 receptor. On the AT2 receptor, ^{125}I-CGP42112A binding could also be fully displaced by angiotensin 1-7 (pKi 6.55). Strikingly, dAla-angiotensin 1-7 could displace AT2 binding (pKi 4.73) but had no effect on AT1 binding up to 100 µM.
Based on these data, we suggest that angiotensin 1-7 is in fact acting via AT2 receptors. The physiological properties of AT2 receptor and those of angiotensin 1-7 are similar, and the binding data show that ^{125}I-CGP42112A could be fully displaced by both angiotensin 1-7 and its antagonist.

Wouter Kamphuis, Target Biology Unit, Solvay Pharmaceuticals, C.J. van Houtenlaan 36, 1381 CP Weesp, t 0294-449114, e-mail wouter.kamphuis@solvay.com

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