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Meeting abstract

Transactivation within the AT_1 angiotensin receptor homodimer: the role of the conserved DRY motif

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Background

The concept of 7TM receptor dimerization has been well established. However, the mechanism and the functional consequences of dimerization are not known in detail. Recent data showed that interaction within the receptor dimer depends on G protein coupling.

Methods

In this study we examined the possible functional consequence of transactivation within angiotensin AT_1 receptor homodimers. To do this, we used the S109Y mutant of the AT_1 receptor, in which the binding site of the nonpeptid AT_1 receptor antagonist, candesartan, was destroyed. Expressing this mutant receptor together with the wild-type in CHO cells, in the presence of candesartan, we could examine the interaction between them by stimulating the S109Y mutant receptor, and following the activation of the wild-type receptor. To monitor the signaling of the receptor two parameters were measured: the conformational change of the receptor using an intramolecular sensor, and the binding of β-arrestin-2 to the activated receptors. In both cases the highly sensitive method of bioluminescence resonance energy transfer (BRET) was applied. Additionally, we performed a radioactive ligand binding assay to examine the cooperativity between receptor monomers.

Results

Under these conditions, we were able to record the activation of the wild-type receptor, which can be explained by the occurrence of the receptors in the form of di- or multimers, with a functional interaction (transactivation) within the complex. This transactivation did not depend on the phosphorylation of the donor receptor, because using the DRY/AAY mutant of the receptor, which is known to inhibit the G protein coupling, resulted in the disappearance of this phenomenon. The radioactive ligand binding data showed increased binding of angiotensin II when the DRY/AAY mutant was expressed compared to the wild-type.

Conclusion

The results also suggest that the interaction between the monomers depends on the presence of the DRY/AAY mutation.