Active-state of AT1 receptor attenuates inverse agonism of ARBs through changes in specific ligand-receptor interactions

G protein - coupled receptors (GPCRs) constitute one of the largest gene superfamilies in the human genome. The angiotensin II (Ang II) type 1 receptor (AT1R) belongs to G - protein coupled receptor (GPCR) superfamily. Typically Ang II activates the AT1R and plays vital roles in cardiovascular and renal pathophysiology. However, several studies have demonstrated that mechanical stress and AT1R-directed autoantibodies can activate AT1R in absence of Ang II-binding (Fig. 1). Both modes of ligand-independent activation of AT1R may occur clinically as in hypertension, cardiac overload conditions or in preecclampsia which can be reduced by actions of inverse agonists with variable efficacies. Ligand-independent AT1R activation is known to attenuate inverse agonistic efficacy of the ARBs but the molecular mechanism was unclear. Recently, we proposed a potential molecular mechanism for attenuated inverse agonism of the ARBs for activated-state AT1R.

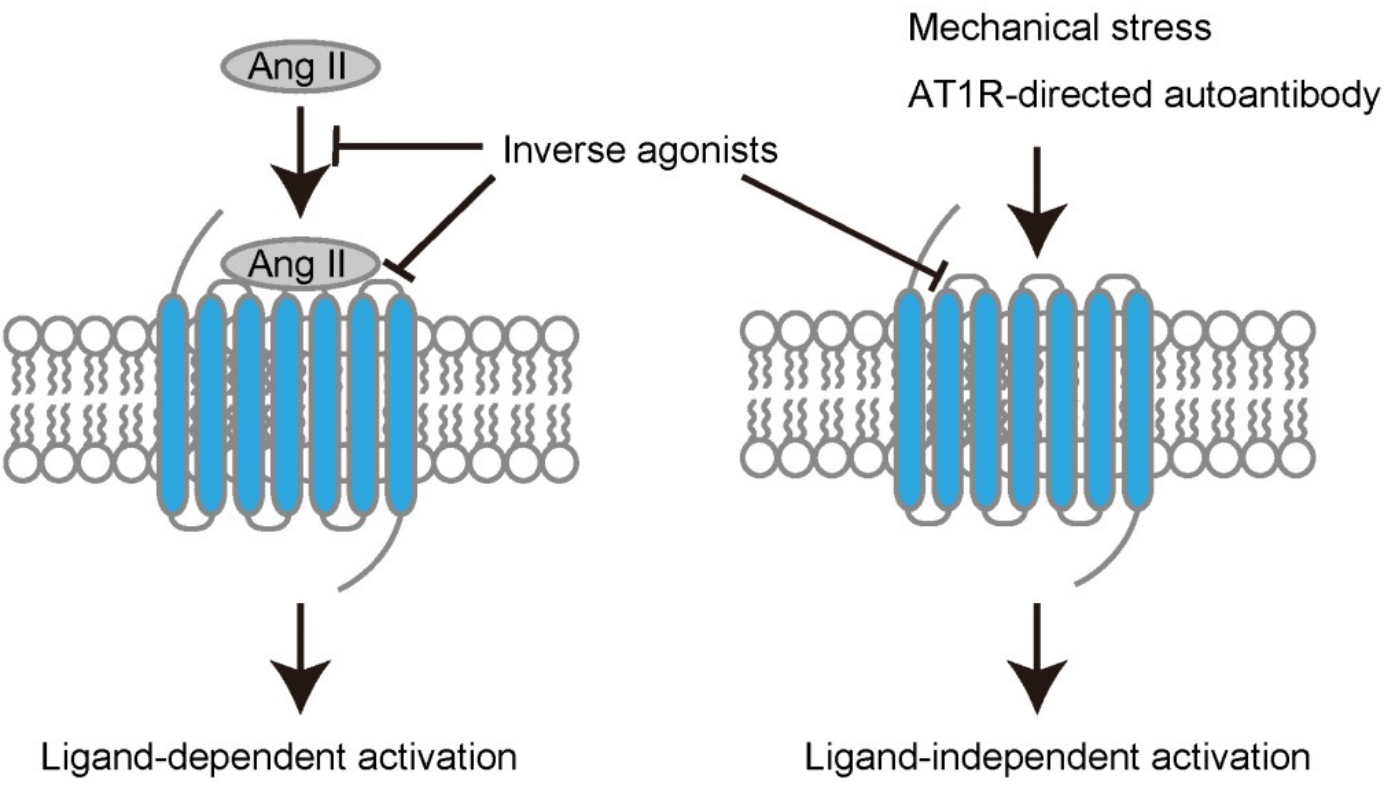

Fig. 1.

Recently solved crystal structure of the human AT1R allowed us to analyze docking models of Losartan, EXP3174, Valsartan and Irbesartan in the AT1R. Canonical ARB binding pocket of AT1R consists of interacting residues of transmembrane (TM)-helices I-VII as well as mainly from second extracellular loop (ECL2). The tetrazole group, a common acidic moiety present in four ARBs, interacts with Arg167. The amino group of Lys199 can form salt bridges with acidic moieties of ARBs or participate in water-mediated interactions with biphenyl scaffold in ARBs. The imidazole ring of Losartan and EXP3174 and equivalent substituents in Irbesartan interact with Trp84 and floor of the ligand pocket including residues Tyr292 and Asn295. The N-acylated valine residue of Valsartan that is equivalent substituents for imidazole ring does not interact with Trp84 but interact with floor of the ligand pocket including residues Tyr292 and Asn295. The short alkyl tails of four ARBs interact with Tyr35, and the biphenyl rings of four ARBs interact with Val108 and Ser109 as well as with Trp253 and Gln257.

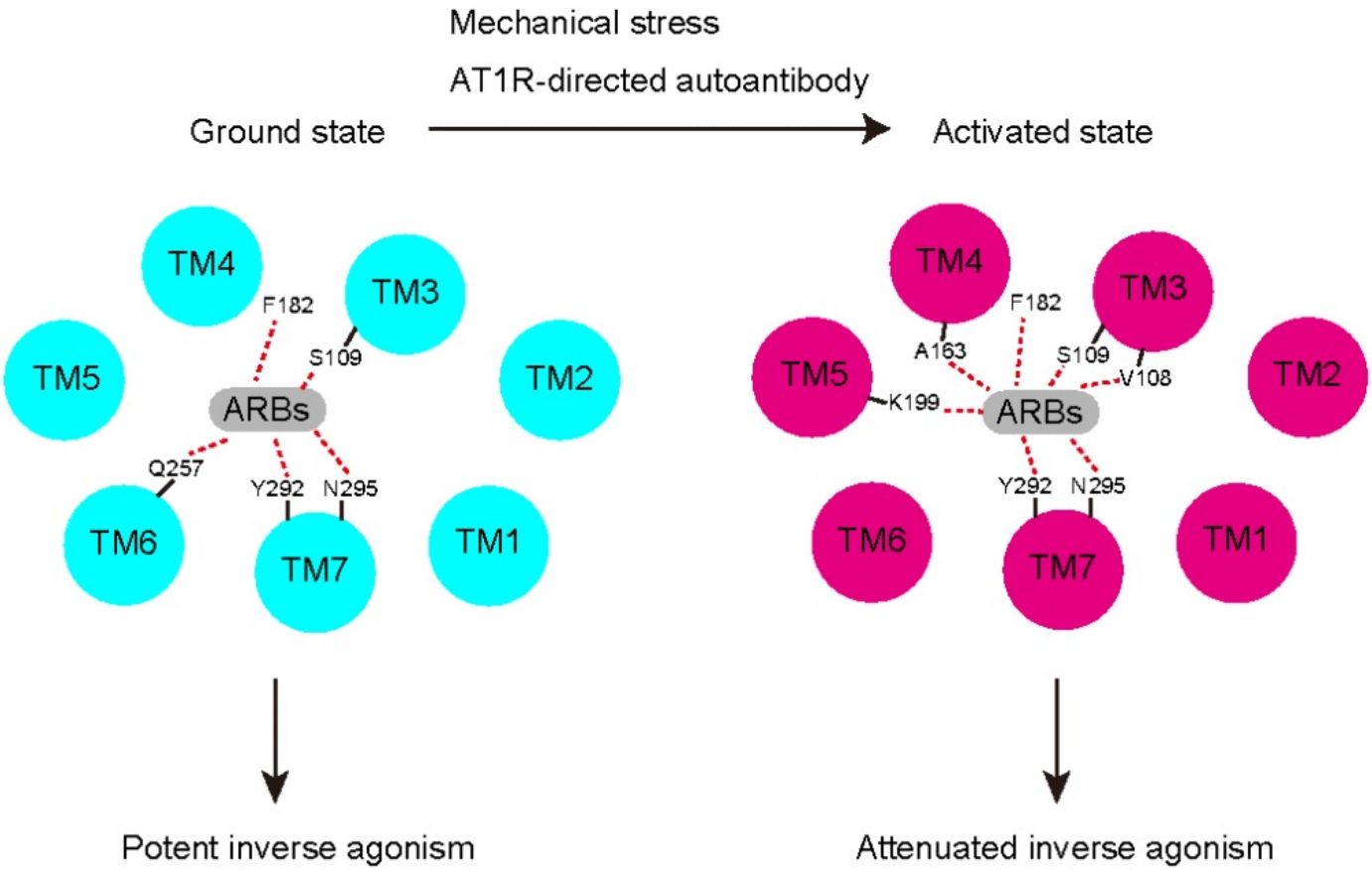

Fig. 2.

In addition, four ARBs may hydrophobically interact with the residues, Tyr113, Phe182, Tyr184 and His256. The crystal structure of human AT1R demonstrated that a hydrogen bond (H-bond)

between Asn111 and Asn295 stabilize the AT1R in an inactive state. We propose that the tight interaction of four ARBs with a set of residues Ser109, Phe182, Gln257, Tyr292 and Asn295 constrains this network, thereby leading to stabilize inactive state of the receptor- and results in potent inverse agonism in the ground state of the AT1R (Fig. 2). On the other hand, the AT1R transitioning toward activated state attenuate the inverse agonism of the ARBs through changes in the ARB-AT1R interactions. Active-state transition in AT1R shifts the ARB-AT1R interactions to a different set of residues, Val108, Ser109, Ala163, Phe182, Lys199, Tyr292 and Asn295, which results in attenuated inverse agonist efficacy of the ARBs (Fig. 2).

ECL2 is known as an important regulator for ligand entry and the receptor function in various GPCRs. In the AT1R the ECL2 was shown to assume an open conformation in ligand free state and assume a lid conformation in the Losartan-bound state, Candesartan-bound state and the Ang II-bound state, suggesting that the ECL2 regulates the conformational state of the AT1R. Our study indicates that the ECL2 residues, Arg167, Glu173 and Phe182 are important regulators of ligand entry and functional property for the AT1R.

Our study could provide a fundamental aspect for application of ARBs in treatment of diseases as well as for novel drug development. Novel ARBs could be more therapeutically relevant than the current commercially available ARBs for treating clinical conditions in which ligand-independent activation of AT1R may be prevalent.

Publication

Structure-Function Basis of Attenuated Inverse Agonism of Angiotensin II Type 1 Receptor Blockers for Active-State Angiotensin II Type 1 Receptor.
Takezako T, Unal H, Karnik SS, Node K
Mol Pharmacol. 2015 Sep