ARBS and adrenal aldosterone: the βarr1 connection

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Aldosterone is produced and secreted by the adrenal cortex in response to angiotensin II (AngII) acting through its AT_1Rs, which are endogenously expressed in adrenocortical zona glomerulosa (AZG) cells [1, 2]. AT_1R is a G protein-coupled receptor (GPCR) that also signals through G protein-independent pathways, a plethora of which are mediated by the scaffolding actions of βarrs (βarrs), originally discovered as terminators of GPCR signaling [3]. AngII elicits aldosterone synthesis and secretion via both G proteins and βarrs (specifically βarr1) [4-6]. Of note, the prototypic drug of the ARB class losartan appears ineffective at blocking the adrenal βarr1-dependent aldosterone production and hence, at suppressing circulating aldosterone [5]. This phenomenon (i.e. failure at suppressing aldosterone) has been observed with several angiotensin receptor blockers (ARBs) clinically and is sometimes referred to as “aldosterone breakthrough” [7-10]. Together, these findings prompted us to investigate the relative potencies of all ARBs at inhibiting these two signal transducers activated by the AT_1R and, consequently, gauge their efficacies at lowering aldosterone in vitro and in vivo.

By using two different but complementary cell-based assay systems, we were able to verify that none of the marketed ARB drugs displays any agonist (or inverse agonist) activity for either G proteins or βarrs at the human AT_1R. In other words, none of them causes activation of either G proteins or βarrs intrinsically [11]. Next, we tested the relative potencies of the drugs at inhibiting βarrs vs. G proteins at the AngII-bound AT_1R and we were able to calculate their relative potencies for βarr and G protein inhibition in vitro. The drugs not belonging to the biphenyl-tetrazol derivatives subclass (azilsartan, telmisartan, and eprosartan) were all equipotent at blocking G proteins and βarrs, displaying “zero” selectivity in their AT_1R inhibition with respect to one signal transducer over the other. Among the tetrazolo-biphenyl-methyl derivatives however, losartan and irbesartan were extremely weak βarr inhibitors, being essentially G protein-specific inhibitors [11]. In contrast, valsartan and candesartan were extremely potent at blocking both βarrs and G proteins [11]. Next, we examined the impact of this on the physiological effect of AT_1R-induced aldosterone production in vitro. Using the human AZG cell line H295R, transfected to overexpress βarr1 [4], and in vitro aldosterone secretion as the readout, we found that candesartan and valsartan are by far the most potent aldosterone secretion inhibitors in vitro [11]. Olmesartan also displays some limited capability of suppressing secretion but losartan and irbesartan are
completely incapable of suppressing SII-induced aldosterone secretion from these cells \(^{11}\). Consistent with these findings, candesartan and valsartan were also the most potent inhibitors of aldosterone synthesis, whereas losartan and irbesartan were completely incapable of reducing aldosterone synthesis in H295R cells \(^{11}\).

From the medicinal chemistry point of view, a substitution both bulky and negatively charged on the biphenyl-tetrazolo-backbone (as in candesartan and valsartan) appears to confer strong \(\beta\)arr inhibition at the AT\(_{1}\)R; losartan and irbesartan have bulky but unionized R\(_{1}\) substitutions (and are weak \(\beta\)arr inhibitors).

In conclusion, by comparing all the ARBs currently on the market head-to-head, candesartan and valsartan appear the most potent \(\beta\)arr antagonists at the AT\(_{1}\)R, in contrast to irbesartan and losartan, which are mainly G protein-selective antagonists, with very low potency at \(\beta\)arr inhibition. These findings translate into candesartan and valsartan having the best efficacy at suppressing aldosterone secretion in vitro, whereas irbesartan and losartan display the worst efficacy at doing so. Given the significant role of the brain renin-angiotensin-aldosterone axis in maintaining sympathetic hyperactivity, development of central hypertension and of cardiac adverse remodeling in heart failure \(^{12}\), these findings may have important consequences for CNS pathophysiology and cardiovascular therapy.

**Conflicting interests**

The author declares no competing financial or any other interests or any relationship with the industry.

**References**