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Angiotensin II type 1 receptor antagonists in animal models of vascular, cardiac, metabolic and renal disease

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ABSTRACT

We have reviewed the effects of angiotensin II type 1 receptor antagonists (ARBs) in various animal models of hypertension, atherosclerosis, cardiac function, hypertrophy and fibrosis, glucose and lipid metabolism, and renal function and morphology. Those of azilsartan and telmisartan have been included comprehensively whereas those of other ARBs have been included systematically but without intention of completeness. ARBs as a class lower blood pressure in established hypertension and prevent hypertension development in all applicable animal models except those with a markedly suppressed renin–angiotensin system; blood pressure lowering even persists for a considerable time after discontinuation of treatment. This translates into a reduced mortality, particularly in models exhibiting marked hypertension. The retrieved data on vascular, cardiac and renal function and morphology as well as on glucose and lipid metabolism are discussed to address three main questions: 1. Can ARB effects on blood vessels, heart, kidney and metabolic function be explained by blood pressure lowering alone or are they additionally directly related to blockade of the renin–angiotensin system? 2. Are they shared by other inhibitors of the renin–angiotensin system, e.g. angiotensin converting enzyme inhibitors? 3. Are some effects specific for one or more compounds within the ARB class? Taken together these data profile ARBs as a drug class with unique properties that have beneficial effects far beyond those on blood pressure reduction and, in some cases distinct from those of angiotensin converting enzyme inhibitors. The clinical relevance of angiotensin receptor-independent effects of some ARBs remains to be determined.

Contents

Abbreviations: ACE, angiotensin converting enzyme; AGE, advanced glycosylation end product; ApoE, apolipoprotein E1; ARB, angiotensin receptor blocker; ANG, angiotensin II; AT1R, angiotensin II type 1 receptor; AT2R, angiotensin II type 2 receptor; BP, blood pressure; CHF, congestive heart failure; DOCA, deoxycorticosterone acetate; ERK, extracellular signal-regulated kinase; GFR, glomerular filtration rate; HUVEC, human umbilical vein endothelial cell; IFNγ, interferon-γ; IL, interleukin; i.v., intravenous; i.c.v., intracerebroventricular; L-NAME, L-nitro-arginine methyl ester; MCP, monocyte chemoattractant protein; PPAR, peroxisome proliferator-activated receptor; RAGE, receptor for advanced glycosylation end product; RAS, renin–angiotensin system; RBF, renal blood flow; SHR, spontaneously hypertensive rat; siRNA, small interfering RNA; STZ, streptozotocin; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VSMC, vascular smooth muscle cell.

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1. Introduction

Angiotensin II (ANG) has an important function in the regulation of the cardiovascular system. This largely occurs via its role as a circulating hormone in the renin–angiotensin system (RAS), but it may also involve locally formed ANG as part of a tissue RAS (Tamura et al., 1997b; Fukuda et al., 1999; Bader, 2010; Siragy & Carey, 2010) or, in the central nervous system, as a neurotransmitter (Culman et al., 2002). Angiotensin II type 1 receptors (AT1Rs) mediate many of the physiological and pathophysiological effects of ANG. Thus, AT1R antagonists, also known as angiotensin receptor blockers (ARBs), have become an important drug class in the treatment of arterial hypertension and congestive heart failure (CHF) and for nephroprotection. Following the discovery of the first non-peptidic ARB, losartan (also known as DUP-753 or MK-954, or EXP 3174 for the active metabolite) (Chiu et al., 1990b; Wong et al., 1990b), several other representatives of this drug class have become clinically available. These include azilsartan (also known as TAK-491 or as TAK-536 for its prodrug), candesartan (also known as TCV-116 for the prodrug or CV-11974 for the active metabolite), eprosartan (also known as SK&F 108566), irbesartan (also known as SR 47436 or BMS 186295), olmesartan (also known as CS-866 for the prodrug and RNH-6270 for the active metabolite), telmisartan (also known as BIBR 277) and valsartan (also known as CGP 48,933).

As reviewed previously, the various ARBs have different chemical structures and accordingly use different binding pockets in the receptor, which are associated with differences in dissociation times and, in most cases, apparently insurmountable antagonism (Michel et al., 2013). The physicochemical differences between ARBs also manifest in different tissue penetration, including passage through the blood–brain-barrier. The combination of these factors is associated with differences in pharmacokinetic profile, particularly duration of action. While generally being highly specific for AT1R, some ARBs, particularly telmisartan, are partial agonists at peroxisome proliferator-activated receptor (PARP)-γ. More recently, it was discovered that ARBs, similar to ligands for many other receptors (Kenakin & Christopoulos, 2013), exhibit a property called 'biased agonism' or 'ligand-directed signaling' (Tilley, 2011; Wilson et al., 2013). This means that some AT1R antagonists can inhibit canonical signaling via the G_q/phospholipase C pathway but may be agonists for other signaling pathways such as β-arrestin pathways. Emerging examples of a potential clinical relevance of this phenomenon are discussed in Section 4.3.3.

While ARBs are mostly known for their effects in the cardiovascular system, they can also affect the function of other organ systems. Such additional effects may occur as a result of vasodilation, often assessed as blood pressure (BP) lowering or, at least in part, independently of it. All clinically used ARBs have high selectivity for AT1R over angiotensin II type 2 receptors (AT2R) as shown for azilsartan (Ojima et al., 2011), candesartan (Shibouta et al., 1993), eprosartan (Keiser et al., 1995), irbesartan (Cazaubon et al., 1993), losartan (Chiu et al., 1990a), olmesartan (Mizuno et al., 1995), telmisartan (Wienen et al., 1993) or valsartan (Criscione et al., 1993). Most ARBs have also high selectivity for AT1R as compared to molecular targets outside the RAS. Notable exceptions include interaction with some types of potassium channels reported for candesartan, eprosartan, losartan and telmisartan, but all of these occur at much higher concentrations than those needed for AT1R occupancy and in none of these cases clinical correlates have been reported (Michel et al., 2013). Some ARBs, i.e. irbesartan, losartan and telmisartan, can inhibit thromboxane A_2 receptor-mediated effects in blood vessels and platelets, and some data suggest that this may be explained by direct interaction with that receptor (Monton et al., 2000). Based on molecular modeling studies, it has been proposed that some ARBs may also bind to vitamin D receptors and chemokine CCR2 receptors (Marshall et al., 2006) but this has not been substantiated experimentally. Several ARBs are substrates of transporter molecules such as P-glycoprotein or members of the Organic Acid Transporting Polypeptide family, which may play a role in their pharmacokinetic profile including penetration into the brain (Michel et al., 2013). For instance telmisartan may inhibit P-glycoprotein, which may lead to drug-drug-interactions (Stangier et al., 2000), and losartan (but not EXP 3174) and candesartan can interact with uric acid transporters, leading to decreases or increases in serum uric acid levels by losartan and candesartan, respectively (Nakashima et al., 1992; Manolis et al., 2000). Uric acid is a substrate of several transporters including OAT1, OAT3, OAT4, and MRP4 (Sato et al., 2008) and the glucose transporter, GLUT9 (also known as URATv1) (Anzai et al., 2008). Although the results for any given transporter have not been fully consistent across ARBs and individual transporters, effects on uric acid transporters have been shown for candesartan (Yamashita et al., 2006; Sato et al., 2008; Nakamura et al., 2010), eprosartan (Edwards et al., 1996), irbesartan (Nakamura et al., 2010), losartan (Edwards et al., 1996; Yamashita et al., 2006; Iwanaga et al., 2007; Anzai et al., 2008; Sato et al., 2008), olmesartan (Iwanaga et al., 2007; Sato et al., 2008), telmisartan (Iwanaga et al., 2007; Sato et al., 2008; Nakamura et al., 2010) and valsartan (Yamashita et al., 2006; Iwanaga et al., 2007; Anzai et al., 2008; Sato et al., 2008). Such interactions of most members of this drug class apparently contribute to clinical effects of at least some ARBs on serum uric acid (Nakashima et al., 1992; Manolis et al., 2000; Sato et al., 2008).

The potentially most relevant molecular interaction of some ARBs with a target other than the AT1R is that with PPARs, specifically PPAR-γ. The most direct evidence for the interaction of some ARBs with PPAR-γ comes from studies demonstrating direct binding of azilsartan, candesartan, irbesartan, losartan and telmisartan to this receptor (Erbe et al., 2006; Storka et al., 2008; Kakuta et al., 2014). This molecular interaction can be associated with partial PPAR-γ agonism, for which telmisartan appears to show the most potent effects (Michel et al., 2013; Kakuta et al., 2014). The potential involvement of PPAR-γ in ARB effects is often studied using inhibition by the PPAR-γ antagonist GW9662 (Willson et al., 2000) or PPAR-γ knock-out (Rong et al., 2010) or knock-down approaches (Nakaya et al., 2007; Scalera et al., 2008; Walcher et al., 2008).

Thus, alteration of a given cell or tissue function by an ARB suggests but does not prove AT1R involvement in the regulation of that function, unless such effects have been demonstrated for multiple members of this drug class. On the other hand, lack of effect of an ARB does not necessarily exclude a role for ANG acting via other receptor subtypes such as AT2R. Based on the typically observed increase in ANG upon treatment with an ARB, ARB treatment may actually enhance AT2R activation. Against this background we have aimed to systematically review the effects of ARBs in non-clinical models, particularly related to disease states of the cardiovascular system, metabolism and the kidney. Based on a cataloguing of these effects we wished to address three main questions:

1. Do ARB effects occur secondary to BP lowering, i.e. are mimicked by other BP-lowering approaches?
2. If not, are they shared by RAS inhibitors as a class, or specific for ARBs as compared to angiotensin-converting enzyme (ACE) inhibitors (Bernstein et al., 2013)?
3. If not, do the effects of some ARBs occur independent of AT1R, i.e. are mediated by other targets?

These findings provide insight into the widespread pathophysiological role of ANG and AT1R activation and also highlight the therapeutic promise of the ARB drug class via and beyond BP lowering.

In the overall interpretation of the data reviewed here it needs to be considered that not all findings can be extrapolated between species, specifically from experimental animals to humans. Reasons may include a species-dependent pathophysiology of a given condition and a different responsiveness to ARBs in some species. For example rabbits may be more sensitive to BP-lowering effects of ARBs than other species as doses typically used in rats may already cause profound hypotension