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Angiotensin type 2 receptors: blood pressure regulation and end organ damage

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In most situations, the angiotensin AT2-receptor (AT2R) mediates physiological actions opposing those mediated by the AT1-receptor (AT1R), including a vasorelaxant effect. Nevertheless, experimental evidence vastly supports that systemic application of AT2R-agonists is blood pressure neutral. However, stimulation of AT2R locally within the brain or the kidney apparently elicits a systemic blood pressure lowering effect. A systemic effect of AT2R stimulation on blood pressure can also be achieved, when the prevailing effect of continuous background AT1R-stimulation is attenuated by low-dose AT1R blockade. Despite a lack of effect on blood pressure, AT2R stimulation still protects from hypertensive end-organ damage. Current data and evidence therefore suggest that AT2R agonists will not be suitable as future anti-hypertensive drugs, but that they may well be useful for end-organ protection in combination with established anti-hypertensives.

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Introduction

It is now generally accepted that the renin angiotensin system (RAS) has many more facets than solely the well-known effects of angiotensin II (Ang II) acting on the AT1-receptor (AT1R). In fact, the RAS harbours several other receptors and hormones (Ang II metabolites) which elicit actions opposing those of the AT1R, resulting in tissue protective effects. Currently known components of the so called 'Protective arm of the RAS' are the hormones angiotensin-(1–7) [1] and alamandine [2], angiotensin converting enzyme 2 (ACE2) [the enzyme responsible for Ang-(1–7) synthesis] [1], and the receptors Mas [for angiotensin-(1–7)], Mas-related G-protein coupled receptor D (MrgD; for alamandine) and the AT2-receptor (AT2R; binding Ang II) [3,4].

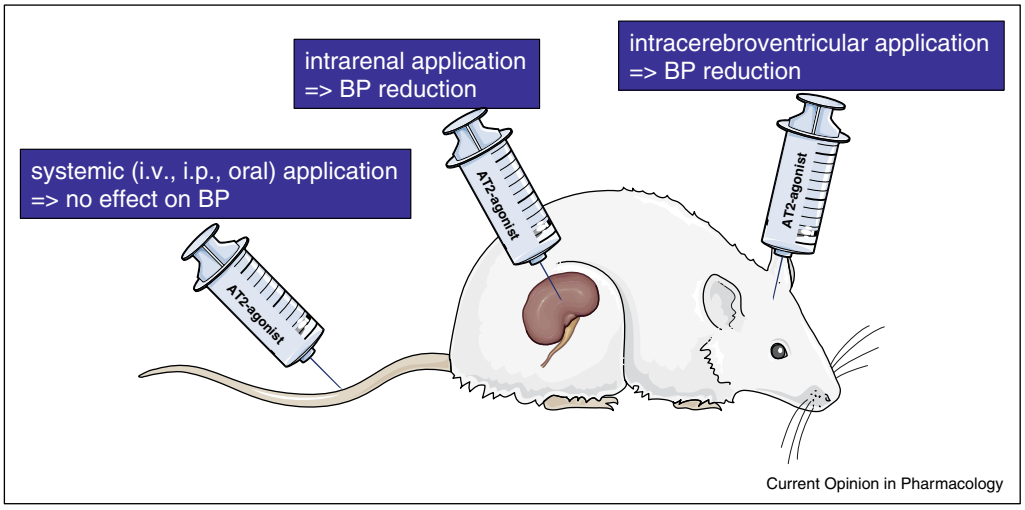
In case of the AT2R, research in recent years has been facilitated and fostered by the availability of a specific and selective non-peptide AT2R agonist, Compound 21 (C21), which for the first time has allowed stimulation of the AT2R in long-term preclinical studies [5]. Using this new research tool, the role of the AT2R in blood pressure (BP) regulation and hypertensive end-organ damage has been re-assessed and studied by several groups [6].

The following article will review studies that have addressed the effects of AT2R stimulation in the periphery, in the brain or the kidney on BP regulation and hypertensive end-organ damage with a focus on findings published during the last two years.

Effects of systemic AT2R stimulation on blood pressure control

Since the AT2R is known to counteract actions of the AT1R by direct (through dimerisation) [7] or indirect (through dephosphorylation) interference with AT1R-coupled signalling [8], it has been assumed that AT2R-stimulation would result in a lowering of BP. This conclusion is supported by multiple studies showing a weak, but consistent vasorelaxant effect of AT2R-stimulation *ex vivo* in isolated vessels originating from various vascular beds such as mesenteric, renal, coronary, cerebral, cutaneous, and uterine arteries [reviewed in 6]. Moreover, AT2R-stimulation has been shown to elicit a strong natriuretic effect [9•,10•,11••]. Nevertheless, the vast majority of studies looking at short-term or long-term effects of AT2R-stimulation did not observe any anti-hypertensive effect. This holds true for models of genetic hypertension (spontaneously hypertensive rats, SHR; stroke-prone SHR, SHR-SP) [12•,13•,14,15••,16••], hypertension induced by inhibition of NO synthesis [17••], by Na^+-overload or volume-overload [11••], for renal hypertension [18•] and for lean or obese normotensive animals [10•,19,20]. Since in some of these models the activity of the RAS (plasma Ang II levels) is suppressed (Na^+-overload and volume overload), while in others it is

Figure 1



The effect of AT2-receptor stimulation on blood pressure is dependent on the route of AT2-recept agonist application. Whereas systemic application (i.v., i.p. or oral) of AT2-receptor agonists is blood pressure neutral (unless the effect is unmasked by low-dose AT1R blockade), application into the kidney or the brain has a blood pressure lowering effect. The figure was created using Servier Medical Art (http://www.servier.com/Powerpoint-image-bank).

rather unchanged (genetic hypertension) or even activated (renal hypertension), the state of activity of the RAS seems to play no role with regard to the efficacy of AT2R-agonists in lowering blood pressure.

However, there are few exceptions, which are as follows (Figure 1):

- AT2R-stimulation in the CNS seems to have a BP lowering effect as discussed in more detail later in this review.
- The BP lowering effect of AT2R-agonists administered peripherally appears to be unmasked when co-administered with a low dose of an AT1R-blocker (ARB), which by itself has no or only a marginal BP lowering effect. This phenomenon has been shown by the groups of Robert Widdop and Robert Carey using peptide or non-peptide AT2R-agonists [16••,21–23]. These data can be interpreted in a way that a constant angiotensinergic tone acting via the AT1R normally dominates over the vasodilatory effect of the AT2R. When an ARB is applied at a high dose, there is no additive effect on BP by concomitant AT2R-stimulation.
- The group of Robert Carey recently reported that in various animal models (volume expansion in rats; Na^+-loaded male and female rats; normal C57BL/6 and AT2R-KO mice) systemic infusion of the AT2R-agonist C21 did not alter BP despite a strong natriuretic and diuretic effect [11••]. However, in female rats chronically (7 days) and systemically infused with Ang II, the resulting elevated BP was markedly reduced when C21 (60 ng/kg/min) was concomitantly infused intrarenally, supporting the existence of an independent, functional, intrarenal RAS [24]. Since in this latter experimental setup several parameters were changed in comparison to the experiments, in which C21 had no effect on BP, it became not entirely clear from this study, what the actual cause for this rather unexpected BP-lowering effect of C21 was. Potential causes could be (a) the model of Ang II induced hypertension, (b) the much longer duration of C21 application (7 days vs 3×30 minutes), (c) the intrarenal route of application, (d) the fact that these experiments were performed in female rats, or a combination of some of these parameters. The assumption that female sex is essential is supported by a series of experiments performed by Kate Denton's group, which showed that adult females express more AT2Rs than males, which leads to lower baseline levels of MAP, but also to a leftward shift of chronic pressure-natriuresis compared to males [12•,25•].
- C21 may have an impact on BP, depending upon whether blood pressure measurements are made in conscious or anaesthetised rats, because there are at least two examples of AT2R-mediated reductions in blood pressure in anaesthetised rats of strains/models (SHR, obese Zucker rats), in which in the conscious state blood pressure was not affected by AT2R-stimulation [13•,16••], while under anaesthesia it was [5,26].

Central nervous system effects of AT2R stimulation on blood pressure control

The overriding view of blood pressure regulation via the RAS within the central nervous system (CNS) begins and ends with pressor and hypertensive effects of Ang II mediated by AT1R [27–29]. This is perhaps not surprising as, according to traditional receptor binding and autoradiography techniques, CNS cardiovascular control areas such as the paraventricular nucleus of the hypothalamus (PVN),