Cardiovascular and renal function of angiotensin II type-2 receptors

Olaf Jöhren *, Andreas Dendorfer, Peter Dominiak

Institute of Experimental and Clinical Pharmacology and Toxicology, University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany

Received 12 September 2003; received in revised form 5 January 2004; accepted 8 January 2004

Time for primary review 29 days

Available online 5 February 2004

Abstract

While all of the well-known cardiovascular and renal effects of angiotensin II (ANG) are attributed to the ANG type-1 (AT1) receptor, much less is known about the function of ANG type-2 (AT2) receptors. This review focuses on progress made in AT2 receptor research over the past 10 years mainly enabled by the availability of AT2 receptor-deficient mice. Two general mechanisms regarding AT2 receptor-mediated actions emerge from recent experiments. Firstly, AT2 receptor stimulation inhibits growth and promotes apoptosis, an important mechanism during development and tissue remodeling. Secondly, ANG stimulates the release of nitric oxide (NO)/cGMP via AT2 receptor activation, as described in the aorta, heart, and kidney. This effect appears to be indirectly mediated by the modulation of bradykinin release. Thus, activation of AT2 receptors may be potentially protective and appears to oppose the effects mediated by AT1 receptors. The question whether AT2 receptors are activated in patients with elevated ANG levels when treated with AT1 receptor antagonists and whether these effects are relevant awaits further clarification.

Keywords: Angiotensin; AT2 receptor; Gene deficiency; Apoptosis; Renal function

1. Introduction

Angiotensin II (ANG) as the main active peptide of the renin–angiotensin system (RAS) acts at specific G-protein-coupled receptors [1]. Based on their selective affinity for peptide and nonpeptide ligands, two ANG receptor subtypes were characterized, namely, subtype-1 (AT1) and subtype-2 (AT2) [2,3]. AT1 receptors are blocked by specific nonpeptide antagonists, such as losartan (DUP 753) and other ‘sartans’, while AT2 receptor antagonists include the non-peptide compounds PD123317 and PD123319 [1–3]. Other AT2 receptor ligands include the peptide agonist CGP 42112 that, however, also binds to nonangiotensin sites particularly during inflammation [1,3,4]. After the initial cloning of AT1 receptors [5,6], AT2 receptor cDNA was isolated by expression cloning from rat fetal tissue [7] and from the rat pheochromocytoma PC12W cell line [8]. The AT2 receptor shares only 34% amino acid sequence homology with the AT1 receptor.

While the role of AT1 receptors in regulation of cardiovascular function, fluid and electrolyte homeostasis, hormone release, and drinking behavior is well established [9], and several AT1 receptor antagonists are now available for the treatment of hypertension, much less is known about the physiological functions of AT2 receptors. AT2 receptors are highly expressed in a variety of fetal tissues [10]. However, although widely distributed in the fetus, the expression of AT2 receptors in adults is low and restricted to certain organs such as the brain, adrenal medulla, kidney, uterus, and ovary [11–14]. The high expression of AT2 receptors during fetal and early postnatal life implies an important role in cellular differentiation and organ development, and experiments using specific agonists and antagonists have provided further evidence for the involvement of AT2 receptors in the regulation of growth, cell proliferation, and apoptosis [1]. Additionally, the observation of elevated blood pressure in AT2 receptor-deficient mice suggested a direct or indirect role of AT2 receptors in the control of cardiovascular and/or fluid homeostasis [15,16]. Two AT2 receptor gene-deficient mouse strains were generated that differ in their genetic background (FVB/N mice [15] and C57BL/6 mice [16]). Here, we summarize current evidence for cardiovascular and...
myocardium

Kidney

vascularity

3. Cardiovascular effects of AT2 receptors

AT2 receptors can couple to multiple intracellular signaling pathways depending on the cell type or cell line expressed (Fig. 1). In cardiac myocytes, proximal tubular epithelial cells, and neuronal cells, ANG stimulates phospholipase A2 (PLA2) activity and arachidonic acid (AA) formation via AT2 receptors [17–19]. In cultured neurons, this effect depends on activation of inhibitory G-proteins and leads to increased delayed-rectifier K+ currents (Ik) that include serine/threonine phosphatase 2A (PP2A) activation and that might reduce neuronal excitability by hyperpolarisation [19–21]. Activation of specific protein tyrosine or serine/threonine phosphatases by AT2 receptors is also observed in various other cell types. In rat pheochromocytoma (PC12W) and mouse fibroblast (R3T3) cell lines, AT2 receptor-mediated growth inhibition and apoptosis involve the activation of mitogen-activated protein kinase phosphatase-1 (MKP-1) [22,23]. In addition, ANG increases MKP-1 activity in adult rat ventricular myocytes [24]. Activation of MKP-1 and PP2A by AT2 receptors results in an inhibition of extracellular-regulated-kinase kinases (ERK) 1 and 2 that appears to be mediated via inhibitory G-proteins [22–27]. In N1E-115 neuroblastoma cells, AT2 receptors inhibit ERK by a G-protein-independent mechanism that involves Src homology 2 domain phosphatase-1 (SHP-1) [28].

The involvement of AT2 receptors in the regulation of cellular cGMP levels by a nitric oxide (NO)-dependent pathway was initially examined in cultured bovine aortic endothelial cells [29]. Stimulation of renal AT2 receptors increases interstitial renal cGMP levels in rats during sodium restriction by stimulation of neuronal nitric oxide synthase (NOS) and subsequent NO production that involves the release of bradykinin [30–32]. Accordingly, in the rat aorta, ANG increases cGMP levels by stimulation of bradykinin and subsequent NO production via AT2 receptors [33] and, in hypertrophied rat hearts, blockade of AT2 receptors results in reduced cGMP levels that augments the growth promoting effect of AT1 receptor stimulation [34]. Recent data also suggest the participation of NO/cGMP- and bradykinin-pathways in AT2 receptor-mediated PC12W cell differentiation and in the inhibition of ANG-induced contraction of rat uterine arteries by AT2 receptors [35,36].

2. AT2 receptor signal transduction pathways

AT2 receptors can couple to multiple intracellular signaling pathways depending on the cell type or cell line expressed (Fig. 1). In cardiac myocytes, proximal tubular epithelial cells, and neuronal cells, ANG stimulates phospholipase A2 (PLA2) activity and arachidonic acid (AA) formation via AT2 receptors [17–19]. In cultured neurons, this effect depends on activation of inhibitory G-proteins and leads to increased delayed-rectifier K+ currents (Ik) that include serine/threonine phosphatase 2A (PP2A) activation and that might reduce neuronal excitability by hyperpolarisation [19–21]. Activation of specific protein tyrosine or serine/threonine phosphatases by AT2 receptors is also observed in various other cell types. In rat pheochromocytoma (PC12W) and mouse fibroblast (R3T3) cell lines, AT2 receptor-mediated growth inhibition and apoptosis involve the activation of mitogen-activated protein kinase phosphatase-1 (MKP-1) [22,23]. In addition, ANG increases MKP-1 activity in adult rat ventricular myocytes [24]. Activation of MKP-1 and PP2A by AT2 receptors results in an inhibition of extracellular-regulated-kinase kinases (ERK) 1 and 2 that appears to be mediated via inhibitory G-proteins [22–27]. In N1E-115 neuroblastoma cells, AT2 receptors inhibit ERK by a G-protein-independent mechanism that involves Src homology 2 domain phosphatase-1 (SHP-1) [28].

The involvement of AT2 receptors in the regulation of cellular cGMP levels by a nitric oxide (NO)-dependent pathway was initially examined in cultured bovine aortic endothelial cells [29]. Stimulation of renal AT2 receptors increases interstitial renal cGMP levels in rats during sodium restriction by stimulation of neuronal nitric oxide synthase (NOS) and subsequent NO production that involves the release of bradykinin [30–32]. Accordingly, in the rat aorta, ANG increases cGMP levels by stimulation of bradykinin and subsequent NO production via AT2 receptors [33] and, in hypertrophied rat hearts, blockade of AT2 receptors results in reduced cGMP levels that augments the growth promoting effect of AT1 receptor stimulation [34]. Recent data also suggest the participation of NO/cGMP- and bradykinin-pathways in AT2 receptor-mediated PC12W cell differentiation and in the inhibition of ANG-induced contraction of rat uterine arteries by AT2 receptors [35,36].

3. Cardiovascular effects of AT2 receptors

ANG regulates blood pressure by controlling vascular tone, either by enhancing smooth muscular tone or indirectly by increasing norepinephrine release, and these effects are mediated via the AT1 receptor [37]. Moreover, neuroendocrine changes, such as activation of the hypothalamic–pituitary–adrenal axis that are associated with essential hypertension, appear also to be related to AT1 receptors [38]. Therefore, the increased basal blood pressure [16,39] and enhanced pressure response in AT2 receptor-deficient mice to ANG [15] and deoxycorticosterone (DOCA)–salt treatment [39] was unexpected and may be related to distinct effects in organs involved in cardiovascular regulation.

3.1. Effects mediated by the central nervous system

Earlier studies suggested the involvement of central AT2 receptors besides that of AT1 receptors in the regulation of

<table>
<thead>
<tr>
<th>Myocardium</th>
<th>Renal functions of AT2 receptors that is primarily based on recent experimental data in these mice (Table 1).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased basal blood pressure</td>
<td>[16,32,39], C57BL/6</td>
</tr>
<tr>
<td>Reduced end-systolic and end-diastolic volumes and reduced heart size</td>
<td>[66], C57BL/6</td>
</tr>
<tr>
<td>Abolished cardiac hypertrophy and cardiac fibrosis after pressure overload or ANG-induced hypertension</td>
<td>[68,69], C57BL/6</td>
</tr>
<tr>
<td>Increased cardiac hypertrophy after myocardial infarction</td>
<td>[70,71], FVB/N</td>
</tr>
<tr>
<td>Increased cardiac rupture after myocardial infarction</td>
<td>[74], C57BL/6</td>
</tr>
<tr>
<td>Reduced survival and increased left ventricular dilatation after myocardial infarction</td>
<td>[70,71], FVB/N</td>
</tr>
<tr>
<td>Reduced urinary sodium excretion and flow rate during chronic ANG infusion</td>
<td>[32,91], C57BL/6</td>
</tr>
<tr>
<td>Reduced pressure natriuresis</td>
<td>[88], C57BL/6</td>
</tr>
<tr>
<td>Increased renal AT1 receptor expression</td>
<td>[88], C57BL/6</td>
</tr>
<tr>
<td>Reduced levels of interstitial fluid bradykinin and cGMP</td>
<td>[32,91], C57BL/6</td>
</tr>
<tr>
<td>Blunted bradykinin and cGMP response after dietary sodium restriction or chronic ANG infusion</td>
<td>[32], C57BL/6</td>
</tr>
<tr>
<td>Increased interstitial fluid levels of prostaglandin E2 (PGE2) and cAMP and reduced levels of PGF2α</td>
<td>[91], C57BL/6</td>
</tr>
<tr>
<td>Enhanced interstitial fibrosis and less apoptotic cells after unilateral ureteral obstruction</td>
<td>[94], C57BL/6</td>
</tr>
<tr>
<td>Anomalies of the urinary tract resembling human congenital anomalies</td>
<td>[93], C57BL/6</td>
</tr>
<tr>
<td>Reduced apoptosis during development of the ureter</td>
<td>[93], C57BL/6</td>
</tr>
</tbody>
</table>

Listed are effects seen in the AT2 receptor-deficient mice when compared with wild-type mice.

<table>
<thead>
<tr>
<th>Systemic effects</th>
<th>Vasculature</th>
<th>Listed are effects seen in the AT2 receptor-deficient mice when compared with wild-type mice.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased arterial neointima formation and smooth muscle cell proliferation after injury</td>
<td>[58], FVB/N</td>
<td></td>
</tr>
<tr>
<td>Increased aortic AT1 receptor expression</td>
<td>[49], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Increased arterial neointima formation and smooth muscle cell proliferation after injury</td>
<td>[58], FVB/N</td>
<td></td>
</tr>
<tr>
<td>Reduced pressure natriuresis</td>
<td>[88], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Increased renal AT1 receptor expression</td>
<td>[88], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Increased arterial neointima formation and smooth muscle cell proliferation after injury</td>
<td>[58], FVB/N</td>
<td></td>
</tr>
<tr>
<td>Enhanced growth of cultured vascular smooth muscle cells</td>
<td>[56], FVB/N</td>
<td></td>
</tr>
<tr>
<td>Increased coronary arterial thickening and perivascular fibrosis</td>
<td>[57], FVB/N</td>
<td></td>
</tr>
<tr>
<td>Reduced survival and increased left ventricular dilatation after myocardial infarction</td>
<td>[70,71], FVB/N</td>
<td></td>
</tr>
<tr>
<td>Reduced urinary sodium excretion and flow rate during chronic ANG infusion</td>
<td>[32,91], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Reduced pressure natriuresis</td>
<td>[88], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Increased renal AT1 receptor expression</td>
<td>[88], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Reduced levels of interstitial fluid bradykinin and cGMP</td>
<td>[32,91], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Blunted bradykinin and cGMP response after dietary sodium restriction or chronic ANG infusion</td>
<td>[32], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Increased interstitial fluid levels of prostaglandin E2 (PGE2) and cAMP and reduced levels of PGF2α</td>
<td>[91], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Enhanced interstitial fibrosis and less apoptotic cells after unilateral ureteral obstruction</td>
<td>[94], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Anomalies of the urinary tract resembling human congenital anomalies</td>
<td>[93], C57BL/6</td>
<td></td>
</tr>
<tr>
<td>Reduced apoptosis during development of the ureter</td>
<td>[93], C57BL/6</td>
<td></td>
</tr>
</tbody>
</table>
drinking behavior and vasopressin release from the hypothalamus [40–43]. In one study, AT2 receptor activation by ANG seemed to oppose the AT1 receptor-mediated stimulation of water intake and vasopressin release [41,42], while others rather showed similar action of both receptor subtypes [40]. Studies in ANG receptor-deficient mice suggest a synergistic effect of AT1 and AT2 receptors regarding ANG-induced water intake [15]. The participation of AT2 receptors in the mediation of hypothalamic ANG effects on hormones was supported by the detection of AT2 receptors in the paraventricular nucleus of the mouse hypothalamus where both AT1 and AT2 receptors are present [43].

Recent data suggest a role of central AT2 receptors in the suppression of baroreflex sensitivity by showing an increased baroreceptor sensitivity and decreased blood pressure variability in AT2 receptor-deficient mice [44]. In rats, ANG was also shown to suppress the baroreceptor reflex via, at least in part, AT2 receptors when injected into the ventral or rostral medulla oblongata [45,46]. However, other authors found only AT1 receptors to suppress the sensitivity of the baroreceptor reflex [47]. Centrally applied ANG increased systolic blood pressure to a greater extent in AT2 receptor-deficient mice than in wild-type mice, and this effect was also blocked by an AT1 receptor antagonist, but was amplified by the AT2 receptor antagonist PD123319 in wild-type mice [48]. These data suggest depressor actions of central AT2 receptors that appear to oppose the pressure response to ANG-mediated via AT1 receptors. In contrast, the increased baroreceptor sensitivity in AT2 receptor-deficient mice [44] would in fact suggest decreased blood pressure in these animals. On the other hand, the elevated blood pressure that was observed in AT2 receptor-deficient mice [16,39] could be caused by various peripheral mechanisms, and it seems likely that in these mice the increased baroreceptor sensitivity reflects rather adaptational changes.

Thus, brain AT2 receptors may play a crucial role in the regulation of blood pressure. However, besides a central regulation of blood pressure via AT2 receptors, cardiovascular and renal effects may also possibly contribute to the elevated blood pressure in AT2 receptor-deficient mice.
3.2. Direct vascular effects

Deletion of the AT2 receptor gene causes an increase in aortic contractility [49,50] which is accompanied by an increased expression of AT1 receptors [49]. Thus, the enhanced acute pressure response to ANG in AT2 receptor-deficient mice may be in part mediated by an increased AT1 receptor expression. However, because the difference in diastolic blood pressure between wild-type and AT2 receptor knockout mice persisted after AT1 receptor blockade with losartan [16] and because the AT2 receptor expression is very low in the adult cardiovascular system, it seems that during development, the AT2 receptor also exerts long-term effects on the vascular structure. In the rat aorta, the expression of AT2 receptors is up-regulated at the late gestational phase and rapidly declines after birth to very low levels in adult animals [51]. Therefore, the involvement of AT2 receptors in vascular development and growth was proposed. Accordingly, the expression of calponin and h-caldesmon, cytoskeleton-associated actin-binding proteins and markers of smooth muscle differentiation, was significantly delayed in AT2 receptor-deficient mice suggesting that AT2 receptors promote the differentiation of vascular smooth muscle cells [52]. Furthermore, in fetal vascular smooth muscle cells, AT2 receptor activation seems to oppose the action of AT1 receptors and enhances apoptosis, an effect that is mediated by activation of the tyrosine phosphatase SHP-1 [27]. A more recent study demonstrated an increased pressure response to ANG and the α1-receptor agonist phenylephrine in vivo and an augmented vasoconstriction of femoral arteries from AT2 receptor-deficient mice not only in response to ANG, but also to norepinephrine and K+-depolarization [53]. This increased vasoconstriction was accompanied by hypertrophy of the media caused by an increase of vascular smooth muscle cells.

A significant role of AT2 receptors in tissue remodeling was also observed after vascular balloon injury. When balloon-injured rat carotid arteries were transfected with the AT2 receptor gene in vivo, the formation of the neointima was significantly reduced [54]. This effect was blocked by treatment with the AT2 receptor antagonist PD 123319. Moreover, transfection of cultured rat vascular smooth muscle cells with the AT2 receptor gene reduced AT1 receptor-mediated cell proliferation in response to ANG [54] and facilitated apoptosis, an effect that was inhibited by AT1 receptor stimulation [55]. Thus, AT2 receptor-mediated effects of ANG seem to be antiproliferative and may counter-regulate growth-stimulating actions mediated by AT1 receptors. These findings were recently supported by studies in AT2 receptor-deficient mice showing enhanced growth of cultured vascular smooth muscle cells [56] and increased coronary vascular remodeling and perivascular fibrosis after aortic banding [57] in the absence of AT2 receptors. Furthermore, in AT2 receptor-deficient mice, the formation of the neointima and the proliferation of smooth muscle cells were greater than in wild-type mice after injury of the femoral artery [58].

As a consequence of AT2 receptor stimulation by elevated ANG levels during AT1 receptor blockade, the kinin–kallikrein system may be activated [59]. Gohlke et al. [33] reported an increased release of aortic cGMP after acute ANG treatment that was blocked by the AT2 receptor antagonist PD 123319. This AT2 receptor effect was abolished by bradykinin B2 receptor blockade as well as by inhibition of nitric oxide synthase. Because cGMP levels were also increased by treatment with losartan and because PD 123319 affected the increase in cGMP levels after ANG/losartan treatment, it was concluded that AT1 receptor blockade stimulates aortic cGMP release by activation of AT2 receptors. ANG at low concentrations inhibits NO production and endothelium-dependent NO-mediated vasodilatation of porcine coronary arteries via AT1 receptors and superoxide production [60]. At higher concentrations, this effect seems to be antagonized by vasodilatory effects via AT2 receptor activation [60]. Thus, ANG might exert opposite effects via AT1 and AT2 receptors that might involve the kinin/NO pathway.

3.3. Cardiac-specific effects

In the human heart, AT2 receptors are the main subtype whereas, in rodents the AT2 receptor expression is low [61]. Moreover, cardiac AT2 receptors are up-regulated in rats and humans under certain pathophysiological conditions, such as myocardial infarction, and are therefore suggested to play an essential role in tissue remodeling [62,63]. In hypertrophy of adult rat hearts, the growth response of the left ventricle to ANG was enhanced by blockade of AT2 receptors [34]. Cardiac-specific overexpression of the AT2 receptor gene in mice reduced the AT1 receptor-mediated enhancement of heart rate and blood pressure [64]. This effect was completely blocked with an AT2 receptor antagonist. In addition, left ventricular systolic function was preserved after reperfused myocardial infarction in these mice [65]. As in the vasculature, increased levels of AT1 receptor mRNA were found in the left ventricles of AT2 receptor-deficient mice [66]. Studies in cultured cardiomyocytes indicate an interaction of AT1 and AT2 receptors in the promotion of apoptosis that might be important for tissue remodeling [67].

AT2 receptor-deficient mice showed smaller end-systolic and end-diastolic volumes in association with a reduced heart size compared to wild-type mice, but no other changes in left ventricular performance were observed [66]. In AT2 receptor-deficient mice, inconsistent results exist regarding cardiac hypertrophy. In one model, deletion of the AT2 receptor prevented left ventricular hypertrophy and interstitial fibrosis after pressure overload or in the case of ANG-induced hypertension and a stimulatory effect of AT2 receptors in cardiac hypertrophy was concluded [68,69]. On the other hand, AT2 receptor-deficient mice with the
FVB/N background acquired greater left ventricular hypertrophy after myocardial infarction than wild-type mice [70,71]. Cardiac-specific overexpression of the AT2 receptor was shown to either reduce perivascular fibrosis in mice treated with ANG for 14 days [72] or to increase fibrosis and heart failure [73]. Thus, various factors, such as experimental settings, sufficient AT2 receptor expression/stimulation, and the genetic background of mice, may contribute to the observed different effects on cardiac hypertrophy attributed to AT2 receptors.

After myocardial infarction, the incidence of death by cardiac rupture and the levels of prostaglandin E2 were increased, while fibrosis and collagen expression were reduced in AT2 receptor gene-deficient mice when compared to wild-type mice [74]. Furthermore, AT2 receptor-deficient mice showed reduced survival and impaired cardiac function after myocardial infarction when compared to wild-type mice [70,71]. In contrast, Xu et al. [75] found no difference in the survival rate and cardiac function after myocardial infarction between AT2 receptor-deficient and wild-type mice but found an improved therapeutic effect of an AT1 receptor antagonist. Interestingly, chronic heart failure after myocardial infarction is similar in mice with or without functional eNOS, but advantageous effects of AT1 receptor antagonists are diminished in eNOS-deficient mice [76]. As in this situation, AT2 receptors may be stimulated by increasing ANG levels; they may stimulate kinin/NO release and may, by blockade of B2 receptors [78]. The aforementioned reduced levels of renal bradykinin and cGMP during development [81–83], and in adult rats AT2 receptors are reexpressed on glomeruli and in interstitial cells during dietary sodium depletion [82].

Renal actions of ANG include the stimulation of vasoconstriction and tubular sodium reabsorption, effects attributed to AT1 receptors. Because of the low amounts of AT2 receptors in the adult kidney, functional analysis of AT2 receptors is difficult to carry out, and the results reported are controversial. ANG-induced renal vasoconstriction was found to be increased in rabbit afferent arterioles [84] or decreased in renal microvessels of rats [85] by the AT2 receptor antagonist PD123319. In rats, AT2 receptor antagonists increased and agonists decreased diuretic and natriuretic effects of high renal perfusion pressure [86,87]. The diuretic and natriuretic actions of renal AT2 receptors are emphasized by the reduced pressure natriuresis in AT2 receptor-deficient mice [88]. In contrast, the diuresis and natriuresis induced by the AT1 receptor antagonist losartan was partly blunted by the AT2 receptor antagonist PD 123319 in spontaneously hypertensive rats [89]. Interestingly, the renal effects of AT1 receptor blockade in this model were also attenuated with icatibant (Hoe 140), a bradykinin B2 receptor antagonist, and by the cyclo-oxygenase inhibitor meclofenamate [89].

In a series of experiments, Siragy and Carey [31] analyzed the function of renal AT2 receptors using a microdialysis technique. During sodium depletion, ANG stimulated the release of renal cGMP via AT2 receptors by increasing nitric oxide. AT2 receptor-deficient mice showed a more pronounced decrease in sodium excretion in response to chronically infused ANG that was associated with markedly decreased levels of renal bradykinin and cGMP compared to wild-type animals [32]. Furthermore, AT2 receptor-deficient mice did not respond to sodium depletion with an increase in renal bradykinin and cGMP [32]. These AT2 receptor actions were mediated by the production of bradykinin and nitric oxide/cGMP [90]. In addition, AT1 receptor-mediated production of renal prostaglandin E2 was enhanced by the AT2 receptor antagonist PD 123319 [30]. These results were also confirmed in AT2 receptor-deficient mice [91], whereas similar experiments in B2 receptor-deficient mice also indicate the possibility of direct stimulation of NO synthesis by AT2 receptor activation [92]. Thus, AT2 receptor stimulation opposes AT1 receptor-mediated antinatriuretic effects of ANG in the kidney and a protective role of renal AT2 receptors was proposed.

AT2 receptors-deficient mice develop an obstructive nephropathy that resembles congenital anomalies of the
kidney and urinary tract in humans [93]. The development of this phenotype is accompanied by a reduced apoptotic activity around the ureter of AT2 receptor-deficient mice at 16.5 gestational days. Moreover, a significant incidence of a mutation in the AT2 receptor gene occurs in human infants with congenital kidney and urinary tract anomalies [93]. Thus, AT2 receptors play an important role for the ontogenesis of the kidney and ureter. Complete unilateral ligation of the ureter results in a more severe fibrosis in AT2 receptor-esis of the kidney and ureter. Complete unilateral ligation of details of AT2 receptor-mediated effects is of great impor-
tance. The questions whether AT1 and AT2 receptors are colocalized at the cellular level and which exact mecha-
nisms mediate a possible AT1–AT2 receptor crosstalk still remain open.

Two general concepts regarding the mechanisms of AT2 receptor actions emerge from experimental data during the past 10 years that were also confirmed using AT2 receptor-deficient mice. Firstly, ANG regulates growth and apoptosis via the AT2 receptor. Secondly, in the aorta, heart, and kidney, AT2 receptor activation stimulates the release of nitric oxide/cGMP and may mediate vascular relaxation. This effect could be indirectly mediated by the modulation of bradykinin release. Thus, a main physiological role of AT2 receptors appears to be the inhibition of cell proliferation and the propagation of cell differentiation during tissue development. In the adult, these AT2 receptor actions seem to be reactivated throughout structural tissue remodeling. By increasing apoptosis and inhibiting growth, AT2 receptors may counter-regulate the growth-stimulating ANG effect mediated by AT1 receptors. However, at present, it is unclear whether AT2 receptor-mediated effects in selected tissues/cell lines and diverse experimental settings could be general-
ized. In addition, the question whether AT2 receptor activation is relevant and of beneficial use in patients treated with AT1 receptor antagonists remains to be clarified in the future.

5. Summary and outlook

Although ANG actions regulating blood pressure were mainly attributed to AT1 receptors, there is convincing evidence that AT2 receptors are also involved at cardiovas-
cular and renal levels. AT2 receptors seem to functionally antagonize ANG actions mediated by AT1 receptors. Be-
cause blockade of AT1 receptors increases the plasma levels of ANG, treatment with AT1 receptor antagonists may lead to AT1 receptor stimulation. Therefore, understanding of the details of AT2 receptor-mediated effects is of great impor-
tance. The questions whether AT1 and AT2 receptors are colocalized at the cellular level and which exact mecha-
nisms mediate a possible AT1–AT2 receptor crosstalk still remain open.

Two general concepts regarding the mechanisms of AT2 receptor actions emerge from experimental data during the past 10 years that were also confirmed using AT2 receptor-deficient mice. Firstly, ANG regulates growth and apoptosis via the AT2 receptor. Secondly, in the aorta, heart, and kidney, AT2 receptor activation stimulates the release of nitric oxide/cGMP and may mediate vascular relaxation. This effect could be indirectly mediated by the modulation of bradykinin release. Thus, a main physiological role of AT2 receptors appears to be the inhibition of cell proliferation and the propagation of cell differentiation during tissue development. In the adult, these AT2 receptor actions seem to be reactivated throughout structural tissue remodeling. By increasing apoptosis and inhibiting growth, AT2 receptors may counter-regulate the growth-stimulating ANG effect mediated by AT1 receptors. However, at present, it is unclear whether AT2 receptor-mediated effects in selected tissues/cell lines and diverse experimental settings could be general-
ized. In addition, the question whether AT2 receptor activation is relevant and of beneficial use in patients treated with AT1 receptor antagonists remains to be clarified in the future.

References

sin II receptor subtypes. Biochem Biophys Res Commun 1989;165:
196–203.
chemical characterization of two angiotensin II receptor subtypes.
205–51.
F922–30.
[12] Jörhen O, Inagami T, Saavedra JM. AT1A, AT1B, and AT2 angioten-
[18] Jacobs LS, Douglas JG. Angiotensin II type 2 receptor subtype medi-
[20] Kang J, Posner P, Sumners C. Angiotensin II type 2 receptor stimu-


[23] Horiuichi M, Hayashi W, Kambe T, Yamada T, Dzau VJ. Angioten-

sion II type 2 receptor dephosphorylates Bel-2 by activating mitogen-


kinases in rat brain neuronal cultures are activated by angiotensin II type 1 receptors and inhibited by angiotensin II type 2 receptors. J Biol Chem 1996;271:15635–41.


[30] Siragy HM, Carey RM. The subtype-2 (AT2) angiotensin receptor regulates renal cyclic guanosine 3′,5′-monophosphate and AT1 re-


[33] Gohlke P, Pees C, Unger T. AT2 receptor stimulation increases aortic


[34] Bartunek J, Weinberg EO, Tajima M, Rohrbach S, Lorell BH. Angioten-


[37] Brach S, Sieroslawski L, Dominiak P. Angiotensin II increases nor-


[40] Hogarty DC, Speakman EA, Puig V, Phillips MI. The role of angio-
tensin, AT1 and AT2 receptors in thepressor, drinking and vasopres-


[42] Höhle S, Spitznagel H, Rascher W, Culman J, Unger T. Angiotensin AT1 receptor-mediated vasopressin release and drinking are poten-

sin-converting enzyme, angiotensin II, angiotensin II receptor sub-


[47] Matsumura K, Averill DB, Ferrario CM. Angiotensin II acts at AT1 receptors in the nucleus of the solitary tract to attenuate the barore-


[50] Akishita M, Yamada H, Horiuichi M. Increased vasconstric-


[59] Dendorfer A, Wolfrian S, Dominiak P. Pharmacology and cardiovas-


[60] Zhang C, Hein TW, Wang W, Kuo L. Divergent roles of angiotensin II


