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Physiological and pharmacological implications of AT_1 versus AT_2 receptors

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Physiological and pharmacological implications of AT_1 versus AT_2 receptors. Angiotensin II (Ang II) has diverse physiological actions that lead, for instance, to increases in extracellular volume and peripheral vascular resistance and blood pressure, and it has also been implicated in the regulation of cell growth and differentiation. Molecular cloning and pharmacological studies have defined two major classes of Ang II receptors, designated AT_1 and AT_2. Most effects of Ang II are mediated by AT_1 receptors. Much less is known about the physiological role of AT_2 receptors. Recent evidence suggests involvement of AT_2 receptors in development, cell differentiation, apoptosis, and regeneration in various tissues. AT_1 and AT_2 receptors have been shown to exert counteracting effects on cellular growth and differentiation, vascular tone, and the release of arginine vasopressin. In each condition, the AT_2 receptor appears to down-modulate actions mediated by the AT_1 receptor, resulting in decreased cellular proliferation, decreased levels of serum arginine vasopressin levels, or decreased vasoconstrictor responses. In addition, in neuronal cell lines, the AT_2 receptor exerts antiproliferative actions and promotes neurite outgrowth, an effect accompanied by significant changes in the expression pattern of growth/differentiation-related genes.

The octapeptide angiotensin II (Ang II) is the major effector of the renin-angiotensin system (RAS) and exerts a wide range of actions. Besides its physiological contribution to cardiovascular, renal, and endocrine functions and its osmoregulatory role in the central nervous system, Ang II plays a major role in the pathogenesis of hypertension and is also considered an important factor in cardiovascular pathology, such as cardiac left ventricular hypertrophy and fibrosis, vascular media hypertrophy, or neointima formation and structural alterations of the heart and kidney, such as postinfarct remodeling and nephrosclerosis. Recently, Ang II has also been implicated in cell growth and differentiation. In the kidney, for example, Ang II is involved in angiogenesis occurring during glomerular differentiation [1] and nephrosclerosis [2]. Furthermore, the role of Ang II as a growth factor has been demonstrated in studies on fibroblasts, adrenal cortical, vascular smooth muscle (VSM), or cardiac cells, and growth-modulating effects have been shown also in mesangial and tubular cells of the kidney [3, 4].

Key words: angiotensin II, angiotensin receptors, renin angiotensin system, receptor antagonists, hypertension, growth factors.

ANGIOTENSIN II RECEPTOR SUBTYPES

The development of highly specific and selective AT_1 receptor antagonists, such as losartan, valsartan, eprosartan, irbesartan, candesartan, telmisartan, and others [5, 6], and AT_2 receptor ligands/antagonists, such as PD123177, PD123319, and CGP42112 [6, 7], was the basis for the identification and characterization of Ang II receptor subtypes. Two main Ang II receptor subtypes have been characterized, AT_1 and AT_2, which are heterogeneously distributed in peripheral tissues and in the brain (Table 1) [5, 8–10]. In humans, only a single gene encoding for the AT_1 receptor is expressed, which is localized on chromosome 3. In rodents, however, AT_{1a} and AT_{1b} receptor isoforms exist, which are localized on chromosomes 17 and 2, respectively. They show 91% similarity for nucleic acid and 96% similarity for amino acids [11, 12]. Although AT_{1a} and AT_{1b} subtypes seem to be more or less equally expressed in spleen, liver, and kidneys [4, 11, 12], the AT_{1a} receptor seems to predominate in VSM, heart, lung, ovary, and hypothalamus [4, 11–14]. The fact that AT_{1a} predominates in VSM suggests that this subtype plays a role in vasoconstriction. On the other hand, as the AT_{1b} receptor subtype seems to prevail in the anterior pituitary, adrenal gland, uterus, and several periventricular brain areas [4, 12–15], this receptor may be involved in hormonal secretion and central osmotic control. In humans and mice, the genes for the AT_2 receptor are localized on the X-chromosome. Both AT_1 and AT_2 receptors belong to the seven-transmembrane-domain superfamily of receptors, but the nucleic acid sequence of the AT_1 receptor has only 34% identity with the AT_2 receptor sequence. The AT_2 receptor is found ubiquitously in fetal tissues. In the adult organism, this receptor is expressed highly in the adrenal medulla, uterus, and ovary, and is also found in vascular endothelium and certain areas of the brain [4, 10, 16, 17]. The fact

Table 1. AT_1 and AT_2 receptors and their distribution

	AT_1 receptor	AT_2 receptor
Distribution	Widely distributed in adult tissues, e.g., blood vessels, kidney, adrenal gland, heart, liver, brain	Widely distributed in fetal tissues, expression in the adult brain, adrenal glands, ovary, uterus, endothelium, myocardium
Function	Vasoconstriction, cardiac contractility, aldosterone release, glomerular filtration, renal blood flow, cardiac and vascular hypertrophy, central osmoregulation	Possible role in growth and development (antiproliferation, inhibition of neointima, cell differentiation)
Structure	Seven-transmembrane-receptor, G-protein-coupling	Seven-transmembrane-receptor, G-protein-coupling
Ligands	Losartan, valsartan, irbesartan, candesartan, eprosartan, telmisartan, tasosartan	PD 123177, CGP 42112A, PD 123319
Isoforms	AT_{1a}, AT_{1b}	?

that the AT_2 receptor is expressed at high levels in embryonic tissues but much less so in normal adult tissues has prompted speculation on its possible role in cell growth and differentiation. The presence of different subtypes for the AT_2 receptor and the existence of AT_3 and AT_4 receptor subtypes are still controversial [18–23].

THE AT_1 RECEPTOR

The AT_1 receptor reportedly interacts with various G proteins and is coupled to one of the two heteromeric G proteins: $G_{q\alpha}$ or $G_{i\alpha}$. Ang II binding to specific sites of the extracellular and membrane-spanning portions of the AT_1 receptor releases the α subunit of the G protein and subsequently activates phospholipase C via G_q or inhibits adenylate cyclase via G_i. Phospholipase C activation generates 1,4,5-inositol trisphosphate and diacylglycerol, with subsequent activation of protein kinase C and an increase in intracellular $[Ca^{2+}]$ via L-type Ca^{2+} channels [24–26]. The rise in intracellular $[Ca^{2+}]$ is accompanied by typical AT_1 receptor-associated responses such as vasoconstriction, renal salt and water retention, aldosterone and vasopressin release, effects on glomerular filtration rate, and renal blood flow, as well as the Ang II-mediated stimulation of cell growth. Protein kinase C and elevated intracellular $[Ca^{2+}]$ promote expression of growth-related inducible transcription factors, such as, c-*fos*, c-*myc*, and c-*jun* [27]. The proteins encoded by the growth-related inducible transcription factors act as transcription factors for various target genes, which may be involved in the stimulation of mitogenesis. Ang II also induces, via the AT_1 receptor, transcription of platelet-derived growth factor-A chain and transforming growth factor-β_1 and so is coupled directly to growth factor expression [28, 29]. It was shown recently that stimulation of AT_1 receptors in VSMcells (VSMCs) induces rapid phosphorylation of tyrosine in the intracellular kinases Jak2 and Tyk2 and that this phosphorylation is associated with increased Jak2 activity [30]. This is significant, because the Jak-STAT pathway may be the signaling mechanism used by cell surface-binding cytokines responsible for transcriptional activation of early growth response genes [31]. This pathway may thus play an additional role in the control of AT_1-mediated cell growth.

VSMCs in culture, a cell line commonly used for studying trophic effects of Ang II, express only AT_1 receptors, and consequently, trophic effects shown in these cells can be mediated only by AT_1 receptors [17]. In all experiments on these cells, AT_2 receptor ligands are ineffective. The growth responses of VSMCs to Ang II vary with the particular VSMC studied, and the mechanisms leading to differential growth responses are still controversial. Dzau et al have proposed that Ang II represents a bifunctional growth factor for VSMCs by simultaneously stimulating proliferative and antiproliferative pathways that appear to be mediated by the activation of platelet-derived growth factor-AA and transforming growth factor-β_1, respectively, thereby shifting the balance in favor of hypertrophy instead of hyperplasia in some instances [32].

Compared with AT_2 receptors, AT_1 receptors dominate by far in the adult human [33] and rat [34] kidneys; only 5% to 10% of the Ang II receptors are AT_2. This predominance of AT_1 receptors might in part explain why angiotensin converting enzyme (ACE) inhibitors and AT_1 antagonists act very similarly in the kidney [35]. AT_1 antagonists can also vasodilate the renal vessels, particularly the glomerular efferent (and afferent) arterioles, increase cortical renal plasma flow [36, 37], and enhance glomerular filtration rate via a contraction of mesangial cells. Beneficial effects, in extent comparable to those of ACE inhibitors, on proteinuria, microproteinuria, and diabetes-induced changes of the kidney have also been described for AT_1 antagonists [38], and in spontaneously hypertensive rats, AT_1 antagonists improve cardiac and vascular structure and function similar to ACE inhibitors [39].

In newborn rat kidneys, AT_1 mRNA occurs in glomeruli, vessels, and nephrogenic cortex, areas where cell proliferation and differentiation occur simultaneously. Blockade of the AT_1 receptor in newborn rats arrests nephrovascular maturation and renal growth, resulting in altered kidney architecture, characterized by fewer, thicker, and shorter afferent arterioles, reduced glomerular size and number,

and tubular dilation [1]. When the mouse AT_{1a} receptor gene is disrupted in embryonic stem cells (AT_1 knockout), however, the deletion is not lethal, and mice are born in expected numbers with normal vasculature, kidneys, and hearts but significantly lower blood pressure [40]. This suggests that the effects of AT_1 receptor blockade on renal structure and function might not only be due to blockade of the AT_1 receptor itself. Actions of the unopposed AT_2 receptor may contribute, as AT_1 receptor antagonists do not affect the AT_2 receptor (and potentially other angiotensin receptor subtypes) but even expose it to increased Ang II levels. The latter is due to the loss of the negative feedback exerted by Ang II via the AT_1 receptor on renin release, and hence on its own generation. It is thus conceivable that under blockade of AT_1 receptors, Ang II interactions with other unopposed Ang II receptors, such as AT_2, are intensified, contributing to the beneficial effects on cardiac and vascular structure seen with AT_1 antagonists [17, 41].

THE AT_2 RECEPTOR

In contrast to the AT_1 receptor, much less is known about the structural and functional properties of the AT_2 receptor. Although this Ang II receptor subtype has been cloned recently [42, 43], its molecular structure and signal transduction pathway are far from completely understood. The rat AT_2 receptor cDNA encodes for a 363-amino acid protein that has a seven-transmembrane topology and 34% homology in nucleic acid sequence to the AT_1-receptor. However, it is still controversial whether the AT_2 receptor is coupled to G proteins and how it signals. Kambayashi et al have reported that the rat AT_2 receptor inhibits a phosphotyrosine phosphatase in COS-7 cells stably expressing the rat AT_2 receptor [42]. This effect is dependent on a pertussis-toxin—sensitive, G-protein—coupled mechanism. Further evidence in support of AT_2 receptor coupling to G proteins has been provided by Kang et al who have shown that G_i (but not G_o) is involved in AT_2 receptor-mediated modulation of K^+ channels in rat primary cultures of neuronal origin [44]. On the other hand, Mukoyama et al have reported that the rat AT_2 receptor shares a seven-transmembrane domain topology that may belong to a unique class of seven-transmembrane receptors for which G-protein coupling has not been demonstrated [43]. In their studies, stimulation of the cloned AT_2 receptor, transiently expressed in COS-7 cells, failed to increase 1,4,5-inositol trisphosphate or intracellular [Ca^{2+}], and no apparent effects on cAMP and cGMP levels or phosphotyrosine phosphatase activity could be observed. In NG 108-15 cells, which express AT_2 receptors constitutively, AT_2 receptor stimulation inhibits T-type Ca^{2+} channels through an as yet undefined pathway [26]. In another cell line, PC12W, which only expresses AT_2 receptors, Ang II stimulates a membrane-associated phosphotyrosine phosphatase and inhibits atrial natriuretic peptide-sensitive particulate guanylate cyclase via a G-protein—independent pathway [28, 45].

The relationship between AT_2 receptor-mediated signaling and tyrosine phosphorylation [42, 45] and the fact that the AT_2 receptor subtype is highly and transiently expressed in fetal tissues followed by a dramatic decrease in most organs just after birth [46] suggests that this receptor plays a role in physiological processes involving cellular growth, differentiation, and adhesion. Recent studies in our laboratory demonstrate that angiotensin peptides can exert an antimitogenic action on rat and bovine endothelial cells of different origin via the AT_2 receptor, suggesting that Ang II has different growth-modulating actions depending on the presence or absence of Ang II receptor subtypes on a given cell [17, 47, 48]. In further studies in PC12W cells, we also demonstrated that Ang II inhibits fetal calf serum- and epidermal growth factor-induced proliferation and potentiated nerve growth factor- and epidermal growth factor-mediated growth inhibition via the AT_2 receptor [41, 49, 50]. This effect is obviously not AT_2-mediated, as c-*fos* and c-*jun* mRNA expression are not inhibited through the AT_2 receptor [51]. Our results are supported by recent findings by Nakayima et al [52] who have attempted to characterize the role of the AT_2 receptor in the model of neointima formation in the balloon-injured rat carotid artery. In this *in vivo* gene transfer study, the AT_2 receptor was transfected to the injured vessel, and the formation of neointima was studied in the presence or absence of the AT_2 receptor. Morphometric analysis performed 14 days after balloon injury revealed that myointimal size was reduced by 70% in the presence of the AT_2 receptor. This effect could be reversed by the AT_2 antagonist PD 123319, suggesting that the expressed AT_2 receptor mediated the inhibiting effect on neointima formation.

Siragy and Carey [53] recently have reported that prostaglandin E_2 $(PGE)_2$ and cGMP levels in the renal interstitial fluid were not altered by AT_1 and/or AT_2 receptor blockade during normal sodium intake in rats. However, under conditions of sodium depletion, the AT_2 antagonist PD123319 inhibited the increase in cGMP engendered by dietary sodium. Treatment with the AT_1 antagonist losartan had no effect on cGMP but significantly decreased PGE_2, whereas PD123319 further increased PGE_2 levels. A combined blockade with losartan and PD123319 decreased both PGE_2 and cGMP. These findings suggest that under conditions of a stimulated renal RAS, but not under normal conditions, the AT_1 receptor promotes renal production of PGE_2, whereas the AT_2 receptor mediates cGMP production. These data imply an interaction between AT_1 and AT_2 receptors with respect to the production and release of these intermediators. These findings are supported by data obtained in spontaneously hypertensive rats, in which AT_2 receptor-mediated stimulation of the bradykinin/nitric oxide system can account for effects of AT_1 receptor blockade on aortic cGMP [54]. Postnatal blockade of AT_2 receptors

in newborn rats does not alter nephrovascular growth or maturation [3], a finding consistent with AT_2 receptors being abundant during fetal life but disappearing soon after birth [46, 55, 56]. Along these lines, AT_2 mRNA in rat kidney is expressed in undifferentiated nephrogenic mesenchymal tissue but not in the immature and mature glomeruli and tubules from day 12 of fetal life to day 15 postpartum, disappearing totally after day 22 postpartum [55, 57]. However, AT_2 receptors can be reexpressed under pathophysiological conditions involving tissue remodeling or repair, such as in vascular neointima formation, postmyocardial infarction, or nerve injury as well as apoptosis [4, 58], to control excessive growth mediated via the AT_1 receptor or by other growth factors. These findings, together with the fact that the AT_2 receptor exerts growth-inhibiting effects on neuronal and endothelial cells [17, 41] and displays a growth-dependent regulation in cultured rat mesangial cells [59], suggest that the AT_2 receptor has general significance for cell growth and differentiation.

SUMMARY

The characterization of the Ang II receptor subtypes offers new tools to advance knowledge on the various functions of Ang II. Recently, AT_1 receptor antagonists have been introduced as orally active antihypertensive drugs. They block AT_1 receptors specifically with low toxicity and high therapeutic safety, and improve cardiac and vascular structure and function similarly to ACE inhibitors. The mechanisms for these additional effects of AT_1 blockers are not yet understood. Besides blood pressure reduction, blockade of the AT_1 receptor may prevent the hypertrophic effects of Ang II with the help of the AT_2 receptor. Furthermore, we could show that Ang II also exerts differential growth-modulating actions depending on the presence or absence of the receptor subtypes on a given cell. Stimulation of AT_1 receptors results in cell growth and/or proliferation, whereas stimulation of AT_2 receptors inhibits cell proliferation. Moreover, there is evidence that AT_1 and AT_2 receptors counteract each other by an as yet unknown mechanism with respect to cell proliferation and differentiation.

APPENDIX

Abbreviations used in this article are: ACE, angiotensin converting enzyme; Ang II, angiotensin II; PGE_2, prostaglandin E_2; RAS, renin-angiotensin system; VSM, vascular smooth muscle; VSMCs, vascular smooth muscle cells.

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