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Future Potential Indications for Pharmacotherapy Using Renin–Angiotensin–Aldosterone System Inhibitory Agents

Nowe potencjalne wskazania do farmakoterapii lekami blokującymi układ RAA

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Abstract
The renin–angiotensin–aldosterone system (RAAS) plays a key role in the pathogenesis of many disorders, including heart failure, coronary artery disease, hypertension, kidney disorders, and diabetic vascular complications. Thus RAAS inhibition using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has become a standard pharmatherapeutic procedure in these clinical entities. Moreover, there are also reports suggesting additional possibilities of ACEI or ARB therapy. Beneficial clinical effects after ACEI or ARB administration were observed in various disturbances, including atherosclerosis, atrial fibrillation, Alzheimer’s disease, post-ischemic stroke state, portal and pulmonary hypertension, and neoplastic disorders. It seems that in the near future these agents may be recommended to inhibit the RAAS in the course of the above clinical entities. However, further studies are required to establish their place in the pharmacotherapy and new potential indications. This article briefly describes the legitimacy of ACEI or ARB treatment of these diseases (Adv Clin Exp Med 2010, 19, 3, 389–398).

Key words: rennin–angiotensin–aldosterone system (RAAS), angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), ACEI and/or ARB novel pharmacotherapy.

Streszczenie

Słowa kluczowe: układ renina–angiotensyna–aldosteron (RAA), inhibitory konwertazy angiotensyny (IKA; ACEI), blokery receptora angiotensyny (ARB), nowoczesna farmakoterapia ACEI/ARB.

The renin–angiotensin–aldosterone system (RAAS) plays one of the most important roles in pathogenesis of many disorders. It regulates cardiac and vasomotor activity (causing an increase in total peripheral resistance and blood pressure) and renal intracapillary pressure together with glomerular filtration rate, maintains optimal salt and water homeostasis, and controls tissue growth. Generally there are two kinds of RAASs: plasma one, associated with central renin release from the
juxtaglomerular apparatus and concerned with general RAAS effects), and tissue RAAS, present in vascular wall and numerous organs, especially in the heart, kidneys, and brain (responsible for local, paracrine regulations). The RAAS is activated in response to threats that compromise blood pressure stability and extracellular fluid volume homeostasis, such as the loss of effective circulating blood pressure, deficiency in the amount of sodium and water, and many clinical entities with unstable hemodynamic conditions (e.g. shock) [1, 2].

RAAS activity is initiated by the release of renin, a proteolytic enzyme, which cleaves angiotensinogen (a liver polypeptide circulating in blood plasma) and transforms it into angiotensin I (AI). Then a second enzyme, angiotensin-converting enzyme (ACE), converts angiotensin I to the powerful biological compound angiotensin II (AII). ACE is found in vascular endothelial cells, lungs, heart, and brain. It must be mentioned that ACE also degrades bradykinin, which has opposite biological effects to angiotensin I, to inactive fragments; thus ACE reduces the plasma level of one of the most important vasodilators. The structure of the RAAS is presented in Figure 1.

AI mediates its effects by two kinds of receptors, AT1 and AT2. AT1 receptor is distributed in the blood vessels, kidney, heart, liver, and brain and AT2 receptor in the adrenal medulla, uterus, ovary, blood vessels, and distinct brain regions. The activation of AT1 leads to systemic and renal vasoconstriction, increased renal sodium reabsorption, vascular smooth muscle growth, oxidative stress and inflammatory cytokine activation, endothelial dysfunction, and increased plasminogen activator inhibitor 1 activity. The biological effects mediated via AT2 stimulation, in contrast, include systemic and renal vasodilatation, decreased renal sodium reabsorption, decreased inflammation, and myocyte hypertrophy with cardiac fibrosis. A short summary of the biological effects observed after AT1 and AT2 stimulation is given in the Table 1.

Moreover, the activation of AI receptors in the zona glomerulosa of the adrenal glands stimulates aldosterone secretion. Aldosterone is a mineralocorticoid which acts via receptors expressed in the kidneys resulting in sodium and water retention; thus it plays an essential role in blood pressure and volume regulation. It is not only under the control of angiotensin II, but its secretion is also mediated by other factors, such as hyponatremia, hyperkaliemia, and hypovolemia. Moreover, it was recently shown that aldosterone is found in other tissues, including heart, brain, and blood vessels, and it contributes to their fibrosis and remodeling (together with angiotensin). It must be noted that there are also non-renin and non-ACE pathways of both angiotensin I and aldosterone formation which can still be active even in the presence of ACE inhibition; this has essential significance during therapy, causing the “ACE escape” phenomenon. Alternative pathways of angiotensin II

Fig. 1. The renin–angiotensin–aldosterone system (RAAS) and its inhibition [1–3]

Ryc. 1. Układ renina–angiotensyna–aldosteron (RAAS) i jego blokowanie [1–3]
Table 1. Effects of angiotensin II receptor activation [1, 2]

<table>
<thead>
<tr>
<th>Mediated through AT1 receptor stimulation:</th>
<th>Skutki aktywacji receptora angiotensyny II [1, 2]</th>
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<tbody>
<tr>
<td>(Wywoływane przez stymulację receptora AT1:)</td>
<td>(Wywoływane przez stymulację receptora AT2:)</td>
</tr>
<tr>
<td>– vasoconstriction (especially coronary, cerebral, renal)</td>
<td>– inhibition of cell growth</td>
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<tr>
<td>– water retention (vasopressin release)</td>
<td>– antiproliferation</td>
</tr>
<tr>
<td>– renin suppression (negative feedback)</td>
<td>– cell differentiation</td>
</tr>
<tr>
<td>– myocyte and smooth muscles hypertrophy</td>
<td>– apoptosis</td>
</tr>
<tr>
<td>– stimulation of vascular and myocardial fibrosis</td>
<td>– vasodilatation</td>
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<tr>
<td>– inotropic</td>
<td>– kidney and urinary tract development</td>
</tr>
<tr>
<td>– chronotropic and arrhythmiogenic</td>
<td>– protection against ischaemia</td>
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<tr>
<td>– stimulation of plasminogen activator inhibitor 1</td>
<td>– systemic and renal vasodilatation</td>
</tr>
<tr>
<td>– thrombosis</td>
<td>– decreased inflammation</td>
</tr>
<tr>
<td>– stimulation of superoxide production</td>
<td>– decreased mitogenesis</td>
</tr>
<tr>
<td>– activation of inflammatory cytokines</td>
<td>– decreased myocyte hypertrophy and cardiac fibrosis</td>
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<tr>
<td>– sympathetic nervous system activation</td>
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Table 2. Effects of RAAS inhibition [3]

<table>
<thead>
<tr>
<th>Skutki blokowania układu RAAS [3]</th>
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<tr>
<td>Lowering of elevated blood pressure</td>
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<tr>
<td>Inhibition of vascular smooth muscles growth</td>
</tr>
<tr>
<td>Regression of ventricular hypertrophy</td>
</tr>
<tr>
<td>Stabilization of left ventricular function after myocardial infarction</td>
</tr>
<tr>
<td>Reduction in renal sodium and water reabsorption</td>
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<tr>
<td>Improvement in proteinuria</td>
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<tr>
<td>Stabilization of renal function in diabetic subjects</td>
</tr>
<tr>
<td>Prevention of heart failure in diabetic subjects</td>
</tr>
<tr>
<td>Reduction of sympathetic nervous system activity</td>
</tr>
<tr>
<td>Stabilization of atherosclerotic plaques</td>
</tr>
<tr>
<td>Normalization of endothelial function</td>
</tr>
<tr>
<td>Enhancement of fibrinolytic activity</td>
</tr>
</tbody>
</table>

effect, i.e. angioedema. It is still unknown whether this adverse effect is shared with other VPIs [1].

It is commonly known and accepted that RAAS inhibition in heart failure [6–10], ischemic cardiac disease [11], kidney disorders [12], hypertension [13], and diabetes [14–16] provides beneficial effects, i.e. the normalization of elevated blood pressure, regression of ventricular hypertrophy, inhibition of vascular smooth muscle growth, stabilization of renal function and improvement in proteinuria (especially in diabetic patients), reduction of activation of the sympathetic nervous system, normalization of endothelial behavior, and enhancement of fibrinolytic activity. These changes put agents inhibiting the RAAS in the center of cardiovascular pharmacotherapy, as mentioned above. This article concentrates further on less known potential applications of RAAS-inhibiting agents.

The Perspectives of RAAS-Inhibiting Agents

RAAS-Blocking Agents in Cardiology – Other Implications

One of the few discussed issues is the potential role of ACEIs in atherosclerotic vascular disease. Apart from their major cardiovascular action, ACEIs are said to have pleiotropic effects. These effects also include their antiatherosclerotic property. There is experimental evidence showing that these agents limited harmful vascular effects and may have an important role in the management of atherosclerotic cardiovascular disease uncomplicated by left ventricular dysfunction, independently of their vasodilating and hypotensive effects. AII is one of many regulatory factors in inflammatory processes, and thus plays an important role in the pathogenesis of atherosclerosis. It interacts with the nitric oxide (NO) pathway and nuclear factor κB (NF-κB) and induces the induction of proinflammatory cytokines [17].

It is confirmed that nitric oxide induces vasodilatation, inhibits the expression of adhesion molecules, and decreases platelet aggregation and smooth muscle cell proliferation. All counteracts NO’s effects by vasoconstrictive action and by reducing NO synthesis. Additionally, AII increases superoxide radical generation by medial smooth muscle cells and oxidative stress changes, which leads to stronger NO synthase inhibition. Chronic NO synthase antagonism increases the levels of superoxide and NF-κB and results in increased AT1 receptor gene transcription. Moreover, NF-κB regulates the expression of many cytokines, chemotactic agents, and adhesion molecules in various inflammatory disturbances and its activity is also co-regulated by factors associated with atherosclerosis, such as oxidized low-density lipoproteins OXY-LDLs. AII increases LDL oxidation in tissue monocytes and thus induces an inflammatory response dependent on NF-κB in vascular smooth muscles. Also, AII, in contrast to NO, induces the expression of adhesion molecules and monocyte chemotactic protein-1 (MCP-1) and increases interleukin 6 (IL-6), transforming growth factor β (TGF-β), and plasminogen activator inhibitor 1 (PAI1) levels, which causes fibrosis and thrombosis. Circulating IL-6 appears to be co-responsible for plaque destabilization by the induction of metalloproteinases, stimulation of the expressions of other cytokines, and the migration and differentiation of mononuclear cells. Thus NO and AII exert opposite effects on endothelial functions both directly and by counteracting each other. Additionally, the high activity of ACE causes prolonged bradykinin degradation, which under normal balanced conditions antagonizes the action of AII [17, 18]. Therefore it may be justified to administer ACEIs (especially those with activity inside vascular tissues) and probably ARBs to all patients with a high risk of ischemic events resulting from atherosclerotic vascular disease, both as primary (i.e. patients without prior adverse disturbances) and secondary prevention (diminishing atherosclerosis progression after cardiovascular event). These beneficial vascular effects preventing vascular morbidity and mortality would follow from the abolition of undesirable AII endothelial effects and favorable NO and bradykinin predominance [17–19].

Another possible property of ACEIs is their antiarrhythmic effect observed in atrial fibrillation (AF). AF is one of the most common supraventric-
ular arrhythmias. According to the Framingham Heart Study, it has a prevalence of 4% in the adult population and as the patient population continues to age, the occurrence of AF increases from < 0.05% of patients 25 to 35 years of age to > 5% of patients > 65 years old [20]. Clinicians attempt to restore normal sinus rhythm with cardioversion and/or treatment with antiarrhythmic drugs. Although cardiac electrostimulation may be appropriate in some patients, pharmacological therapy is the first-line AF therapy. Unfortunately, the classical antiarrhythmic drugs used in this clinical condition (such as encainide, flecainide, sotalol, and others) are associated with risks of ventricular proarrhythmia and increased mortality [21]. However, despite the fact that neither ACEIs nor ARBs are dedicated for primary or secondary AF prevention and treatment, there is accumulating evidence which confirms that these RAAS agents may have antiarrhythmic effects and reduce the risk of cardiovascular events in patients with AF (PROGRESS study). The administration of ACEIs and/or ARBs for conditions for which they are indicated (hypertension, heart failure, diabetic nephropathy) may provide the additional benefit of AF risk reduction. Thus intervening to prevent or delay myocardium remodeling resulting from hypertension or heart failure may prevent AF manifestation. This suggestion is compatible with the etiology of AF; it has a multiplicity of causes ranging from genetic to degenerative, but hypertension and heart failure are the most common and the epidemiologically most prevalent conditions associated with AF.

It seems that the antiarrhythmic properties of ACEIs or ARBs result from their additional profile, mentioned above (anti-inflammatory, antioxidative, reducing cardiac remodeling and fibrosis). This supports the observation about the link between cardiac inflammatory states and AF. Inflammatory infiltrates are often found in the atria of AF patients. Increased CRP and IL-6 plasma concentrations predict AF development. It was also shown that prednisone suppressed AF susceptibility and CRP in animal, methylprednisolone reduced AF recurrence and CRP levels in patients treated with propafenone after conversion of symptomatic persistent AF, and steroids decreased postoperative AF after coronary artery bypass surgery. The participation of oxidative stress in AF’s pathogenesis was indirectly confirmed by water-soluble antioxidant ascorbate administration in human AF, which also revealed beneficial effects [22, 23]. However, the central factor in AF pathogenesis is anatomical and electrical atria remodeling. Angiotensin II is now regarded to be a key element in this phenomenon. In hypertension or heart failure with diastolic dysfunction, cardiac stretch receptors are activated and this triggers locally increased AII synthesis. The density of AII receptors in the atria is generally greater than in the ventricles and this makes the atria more sensitive to AII’s impact. Subsequently, AT1 receptor stimulation causes myocyte hypertrophy, fibroblast proliferation, accumulation of collagen, and apoptosis. Moreover, AII modifies atrial electrophysiology by indirect effects on ion channels, increases calcium influx which augments inflammatory changes, and impairs cell-to-cell coupling associated with gap junction remodeling [24]. Meanwhile, AF pathogenesis is associated with electrical remodeling of the atrium, which provokes a reduction in the refractory period of atrial tissue. In an atrial pacing model of atrial fibrillation, shortening of the atrial effective refractory period (AERP) and loss of rate-adaptive AERP shortening are the main electrical changes associated with AF development. Additionally, the increase in atrial size together with AERP shortening allows functional reentry and a greater tendency to AF arising and its consolidation. Both ACEIs and ARBs were demonstrated to prevent atrial electrical remodeling and reduce rapid atrial pacing independently of the reduction in intra-atrial pressures. Both ACEIs and ARBs were also shown to influence electrical remodeling by significantly reducing the shortening of the AERP [25].

The next supplementary mechanisms by which the antiarrhythmic effect after ARB administration occurs are also said to be secondary to the activation of peroxisome proliferator-activated receptor (which causes anti-inflammatory and metabolic protection) and to their fibrinolytic and antiplatelet properties. Some studies also imply that reduced endothelial nitric oxide (NO) synthetase expression and subsequent local NO production is observed in AF. Reversal of endothelial dysfunction by RAAS blockade could be another beneficial mechanism by which RAAS-inhibiting agents demonstrate their antiarrhythmic properties [24].

In conclusion it should be underlined that there is a growing amount of evidence which supports the important role of the RAAS in cardiac remodeling and AF pathogenesis. Pharmacological RAAS blockade appears to reduce AF, especially in patients with coexistent heart failure, left ventricular dysfunction, and hypertension complicated by ventricular hypertrophy. However, it is premature to recommend the widespread use of ACEIs and ARBs in AF patients. One should expect that the numerous ongoing clinical studies will determine whether their routine use will assume an important place in the pharmacotherapy of atrial fibrillation [26, 27].
RAAS Inhibitory Agents in Neurology

The RAAS is also found in the brain and, what is most interesting, AII is synthesized there independently of peripheral sources. The local brain RAAS, as angiotensin-immunoreactive neurons, was found in two main pathways: a forebrain pathway which connects the circumventricular organs to the median preoptic nucleus, paraventricular, and supraoptic nuclei and a second route connecting the hypothalamus to the medulla oblongata. It was established that AII acting on its AT1 central nervous system receptors influences many physiological responses, causing blood pressure increase, increased drinking and sodium intake, natriuresis, and vasopressin release. Thus the central RAAS is involved in body fluid and cardiovascular homeostasis. Recent findings indicate that overactivity of the brain RAAS (manifested as increased AII content and overexpression of AT1 receptors) may be implicated in the development and maintenance of high blood pressure in spontaneously hypertensive rats. The exact mechanism by which increased brain RAAS activity contributes to hypertension is not known; however, there are suggestions that AII-induced suppression of baroreceptive afferent feedback at the level of the nucleus tractus solitarius and the activation of sympathetic outflow plays a key role. Additionally, angiotensin neurons modify learning and memory and influence neuronal differentiation and nerve regeneration. Several studies revealed positive correlation between cognitive impairment and hypertension. Thus a wide use of ACEIs and ARBs causing blockade of the RAAS in hypertension, heart failure, and coronary artery disease provides an additional advantage. Animal studies also confirm the findings that reduced brain RAAS activity via ACEI or AT antagonists results in an improvement in cognitive functioning. The cholinergic receptor antagonist scopolamine administrated centrally has an opposite effect; thus a reduction of central cholinergic transmission deteriorates cognitive aspects. It was shown that AII decreases potassium-stimulated acetylcholine release from both rat cortex and human temporal cortex. This effect is antagonized by ARB.

What is of special interest, in rats some of the cholinergic neurons and GABAergic cells originate from the medial septal nucleus and AII could inhibit cholinergic transmission via AT1 receptors located on cholinergic cell bodies. Thus AII blockade may increase central cholinergic pathways [28, 29]. This finding is especially important taking into consideration the pathogenesis of Alzheimer’s disease (AD), the most common form of dementia. It was demonstrated that AD is characterized by diminished central cholinergic neurotransmission. AD patients demonstrate elevated levels of AII and ACE activity in the hypothalamus, frontal cortex, and caudate nucleus. Hajjar et al. [30] demonstrated that patients receiving ACEI exhibited a slower rate of AD progression compared with those not receiving ACEI. The exact mechanism by which RAAS agents produce their beneficial effects in patients with AD, apart from their impact on central cholinergic activity, may be also secondary to their pleiotropic effects. ACEIs mediate cerebral blood flow and suppress inflammatory changes and oxygen radical synthesis. ACEIs are also considered to decrease A-β-protein level [31].

The brain RAAS also participates in tissue regeneration and apoptosis and contributes to neuronal injury by initiating and regulating processes known to occur during cerebral ischemia, including inflammation, apoptosis, and impairment of cerebrovascular autoregulation. RAAS modulation restores blood flow after ischemia by normalizing cerebrovascular autoregulation and inhibits ischemia-induced biochemical and metabolic changes. The key place seems to be associated with the AT2 receptor. It is upregulated in rats after global cerebral ischemia, during tissue wound healing, and in dorsal root ganglion neuron and regenerating sciatic nerve after crush injury. These findings suggest that the tissue effects of AII in the brain are dependent on the correct balance between AII and AT2 stimulation. Although the completed mechanisms are still unknown, it seems that RAAS modulation protects against stroke, reduces the volume of brain injury, and improves neurologic recovery from cerebral ischemia. Thus RAAS agents may have a potentially important role in the pharmacologic treatment of stroke [32].

On the other hand, an activated RAAS may also be involved in analgesic effects. It was discovered that microinjection of AI or AII into the ventral of the ventrolateral periaqueductal gray matter (PAG) of rats produces antinociceptive effects. The ARB strongly inhibited the AII-associated antinociception and increased incisional alloe- dynia, which suggests that the antinociceptive effects occurred via the AII receptor in the PAG. The next strong evidence was brought by immunocytochemical studies which revealed the presence of AT receptors in the PAG region. The conclusion may be drawn that locally produced brain AII and peptides acting via AT receptors take part in tonic descending nociceptive control and that administration of ACEI and/or ARB may aggravate pain perception [33].
ACEI in Gastroenterology

There is evidence of profitable effects of RAAS inhibition in portal hypertension. Portal hypertension is one of the most serious complications of chronic liver disease. It is also a main point of pharmacological interest because sustained reduction in portal pressure would reduce its consequences, such as variceal bleeding, hepatic encephalopathy, and ascites development. Until now there are only a few agents used in the treatment of portal hypertension. The treatment of portal hypertension is complex and has both a causal and a symptomatic character. The goal of the causal treatment is focused on the diseases which lead to the portal hypertension and includes some dietetic restrictions, for example decreased of copper intake in Wilson’s disease or iron elimination in hemochromatosis. It is also based on pharmacotherapy, such as nucleoside analogue administration in patients with liver cirrhosis with HBV or liver transplantation in cases of irreversible hepatic disease [34].

Lowering hepatic portal vein pressure together with various endoscopic interventions are the aim of the symptomatic treatment, and a value of < 12 mm Hg is the pharmacological target point (or a decrease from the initial value by > 20%). Nonselective β-blockers (propranolol, nadolol, atenolol) are effective in lowering splanchic blood inflow and are therefore used in the secondary prevention of variceal bleeding; however, approximately one third patients treated with propranolol do not respond despite beta receptor blockade. Other agents used in portal hypertensive therapy are prazosin, clonidine, ritanserin, verapamil, metoclopramide, and domperidone. Alternatively, nitrates such as nitroglycerine and isosorbide mono- and dinitrates are administrated to widen the hepatic sinus vessels, resulting in their hydrostatic pressure decrease. Unfortunately, this may lead to a systemic hypotensive effect and cause neurohormonal system activation and sodium and water retention, sustaining the portal hypertension [34]. Moreover, increased knowledge of the pathomechanisms of portal hypertension involves a new pharmacological target: the reduction of intrahepatic resistance. This is seen as a consequence of activated stellate cell (myofibroblast) contraction. These cells are located in the perisinusoidal space of Disse (mesenchymal cells) and in sinusoidal capillaries (pericytes with smooth muscle features, capable of precapillary contraction). After liver injury they are activated and start to produce increased amounts of extracellular matrix responsible for fibrosis and their function in sinusoidal blood flow is disturbed [35].

It was found that the RAAS is stimulated in patients with liver cirrhosis (the AII plasma level is elevated in cirrhotic patients), being responsible for the effects mentioned above. It is the homeostatic response to counterbalance the vasodilation, arterial systemic hypotension, and renal hypoperfusion in the course of liver cirrhosis. AII causes direct vasoconstriction and enhances the adrenergic vasoconstrictor effect on the portal system and the activation of stellate cells and sodium and fluid retention induced by aldosterone secretion. This is why the RAAS blockade caused by ACEIs or ARBs should be beneficial in improving fluid and salt retention and reducing sinusoidal resistance, resulting in lowering portal pressure [35]. A study comparing the effects of different ACEIs on portal pressure was conducted in patients after endoscopic injection sclerotherapy (EIS), receiving various ACEI agents (groups treated with perindopril, ramipril, fosinopril, lisinopril and captopril and a control group without ACEI administration). Three months after EIS, the portal pressure decreased in all groups receiving ACEI agents, mostly in the group treated with lisinopril [36].

Moreover, there are also reports about bradykinin-dependent liver regeneration when controlled tissue growth and restoration of liver mass to normal conditions are observed. Additionally, the kallikrein-kinin system exerts many biological effects, including vasodilatation, increased vascular permeability, and smooth muscle relaxation and influences cell proliferation. Bradykinin is regarded to be a growth factor for keratinocytes and fibroblasts. Thus bradykinin augmented liver regeneration in a rat model of partial hepatectomy. Because ACE is also a bradykinin-degrading enzyme (also known as kininase II), its inhibition with ACEIs seems to bring profitable effects in liver regeneration. A study by Ramalho et al. showed that ACEIs remarkably increased liver regeneration after 70% hepatectomy in rats. The rate of liver restoration was twice as high in lisinopril-treated and captopril-treated groups than in controls. On the other hand, the administration of a selective AT1 receptor antagonist (losartan) induced lower hepatocyte proliferation compared with controls. These results confirmed the importance of the RAAS in liver cell proliferation and that ACEIs potentiate the biological actions of bradykinin by inhibiting kininase II [37].

RAAS-Blocking Agents in Pulmonology

Another possibility of RAAS-blocking agent use is pulmonary hypertension treatment. Pulmonary hypertension (PH) is characterized by elevated
pulmonary artery pressure and pulmonary vascular resistance. PH etiology is complex, including multiple features, and is therefore usually divided into primary PH, drug-induced PH, hypoxic PH (e.g. in the course of chronic obstructive pulmonary disease or adult respiratory distress syndrome), pulmonary venous PH (pulmonary veno-occlusive disease), thromboembolic PH, and pulmonary capillary vasculature disorders (such as hemangiomatosis). The common pathomechanisms of PH include both abnormal pulmonary vasoconstriction and vascular remodeling. The disturbances observed in PH arise from a wide variety of stimuli: physical (mechanical stretch, shear stress) and chemical (hypoxia, mediators such as angiotensin II, endothelin-I, serotonin, growth factors such as PDGF and bFGF, inflammatory cytokines, and extracellular matrix components and enzymes). There is evidence that AII is co-responsible for the growth of pulmonary artery smooth muscle cells [38]. In PH the overexpression of ACE in the endothelial layer of small pulmonary arteries is observed, leading to the vascular remodeling. Nowadays this seems to be a more important therapeutic target than vasoconstriction. However, the present drugs used in PH treatment are mainly vasodilators, including calcium channel antagonists, prostacyclin PGI2, and nitric oxide. Thus agents targeting pulmonary vascular remodeling or affecting the extracellular matrix are regarded as an interesting alternative approach. These novel drugs include ACEIs together with ARBs, endothelin antagonists and endothelin-converting enzyme inhibitors, phosphodiesterase inhibitors, serine elastase inhibitors, and neutral endopeptidase inhibitors. ACEIs and ARBs were examined in a rat model of PH. It was shown that ACEIs inhibited pulmonary vascular medial thickening and muscularization (although this effect required much higher doses of ACEI than those used in diseases of the systemic circulation) [38]. The beneficial effects of ACEI in pulmonary hypertension were rather due to a decrease in AII than an increase in bradykinin, since treatment with bradykinin receptor antagonist did not bring the desired expected effects. The impact of ARBs on PH was also studied. The AT1 antagonists, similarly to ACEIs, inhibited medial hypertrophy and neomuscularization in hypoxic animals (but AT2 receptor antagonists had no effect on PH development) [39].

RAAS Blockers for Cancer Treatment

There are also several experimental studies indicating that RAAS inhibitory agents may also inhibit tumor growth and development, probably by inhibition of matrix metalloproteinases (MMPs), enzymes involved in extracellular matrix (ECM) degradation. The extracellular matrix is composed of fibrous proteins, mainly collagen, in a hydrated polysaccharide gel which consists of glycosaminoglycans, proteoglycans, and extracellular fluid. The ECM is a diffuse medium allowing the diffusion of hormones and nutrients from the capillaries to the tissue; it contains hormones, growth factors, and cytokines and thus contributes to the modification of tissue function. The major enzyme classes responsible for ECM remodeling are MMPs (serine, cysteine, and aspartic). MMPs are synthesized as pro-enzymes by fibroblasts, inflammatory cells, and some tumor cells. In normal tissues the enzymes are expressed at low levels, but during some physiological and pathological remodeling processes (bone remodeling, wound healing, arthritis) they are overexpressed. Many human tumors also exhibit high MMP levels and there is positive correlation between MMP activity and tumor grade and survival. MMPs are necessary for cancer migration and metastasis and are involved in cancer cell proliferation, adhesion, angiogenesis, differentiation, and apoptosis. Inhibition of MMPs is considered to be a potential modality in novel cancer treatment. There are several synthetic MMP inhibitors (MMPIs) which demonstrated growth retardation and metastasis inhibition in both in vitro cancer cells lines and in animal cancer models of early-stage tumors. Moreover, the combination of conventional chemotherapeutics and MMPIs revealed additive or synergistic effects compared with chemotherapy alone. Marimastat and batimastat were the first MMPIs discovered and applied in animal studies and phase III clinical studies are now underway. MMP inhibition was also observed after captopril and lisinopril treatment. The mechanism of MMP blockade is probably by competitive binding of zinc in the active site of the MMPs (ACE is also a metalloproteinase containing zinc in the catalytic center) [40].

There are also other links between the RAAS and carcinogenesis. AII is a peptide stimulating cell growth, proliferation, and collagen matrix formation via AT1 receptor. AT2 receptor activation stimulates cell differentiation and apoptosis. Some ACEIs were studied to determine their anti-proliferative effect. Captopril and enalapril had anti-mitotic activity in selected tumor line cells. Captopril also had a dose-dependent inhibitory effect on cell migration and invasion in a human glioma cell line. Moreover, capillary endothelial cell migration induced by bFGF was inhibited by captopril, lisinopril, and enalapril, whereas AT1
and AT2 receptor antagonists had no effect. These findings suggest that cell migration is dependent on various stimuli and the inhibition of cell migration by ACEIs could be related to the different intrinsic properties of these drugs. Captopril and perindopril showed inhibition of neovascularization in hepatocellular tumors in mice and decreased expression of VEGF-mRNA in the BNL-HCC cell line. In one mouse study, captopril decreased the number of lung metastases, especially in combined treatment with batimastat. The combination of the available promising experimental findings and the fact that ACEIs are well known pharmacologically and toxicologically suggest that they should be further investigated in prospective clinical trials of cancer patients [40]. Additionally, further experimental studies are needed to explain the mechanisms by which ACE inhibitors and probably other agents blocking the RAAS demonstrate their antineoplastic effects.

References


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