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Significance of the Renin-Angiotensin System in Clinical Conditions

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Abstract

The renin-angiotensin system, in both its circulating and local tissue roles, is intertwined with multiple other regulatory and signalling mechanisms in various tissues and organ systems. It plays a central role in the normal regulation of arterial blood pressure and in the development of hypertension, which is an immense global public health burden and a crucial modifiable risk factor in the development of cardiovascular diseases. The renin-angiotensin system plays also important roles in a range of other clinical conditions such as heart failure, kidney failure, diabetes mellitus and others. Therapeutic interventions within the renin-angiotensin system include the use of medications such as angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists, which are well established and have been invaluable as clinically effective tools during many years of practical use. Additionally, numerous other therapeutic approaches targeting components of the renin-angiotensin system have been developed or are currently in development. This chapter will discuss details of the roles of this system in the most relevant clinical conditions.

Keywords: renin-angiotensin system, hypertension, heart failure, angiotensin-converting enzyme inhibitors, diabetes mellitus

1. Introduction

The renin-angiotensin system (RAS), in both its circulating and local tissue roles, is intertwined with multiple other regulatory and signalling mechanisms in various tissues and organ systems. It is thereby involved in a number of clinical disorders with complex pathophysiological mechanisms. This chapter aims at providing a brief overview of the most relevant conditions in clinical practice in which the RAS is important when considering its pathophysiological or therapeutic significance.

2. RAS in hypertension

Systemic arterial hypertension is the most crucial global modifiable risk factor for morbidity and mortality and clearly connected to cardiovascular

disease development [1]. The RAS plays a central role in the normal regulation of blood pressure and in the development of hypertension [2]. RAS regulates blood pressure through its effector protein angiotensin II (Ang II), which causes the constriction of the efferent arteriole in the kidney glomerulus, as well as the vasoconstriction of arterioles in peripheral circulation [3]. In addition to the above, RAS achieves its effects by stimulating the secretion of aldosterone by adrenal glands and vasopressin by the posterior pituitary, which, through the synergistic effect of water retention and sodium absorption, ensures the stability or increase of the intravascular volume [3]. Abnormal RAS activity is present in conditions such as hypertension and diabetes, which causes slow, continuous damage to the renal parenchyma and leads to the development of chronic kidney disease (CKD) [4, 5].

The pathophysiology of essential hypertension and other types of hypertension is extremely complex and not fully elucidated, with the RAS contributing only in part to the multifactorial pathophysiological mechanisms [1]. There is a pathophysiological interplay between the RAS, endothelial function/dysfunction, the role of the sympathetic nervous system, natriuretic peptides, inflammation and the immune system [1]. A dysfunction in the factors that contribute to blood pressure control may lead to the development of increases in mean blood pressure [1]. The genetic background/predisposition is of course very relevant. Furthermore, the RAS may play a completely different role depending on the type of hypertension. For instance, in primary aldosteronism, the most common type of secondary hypertension, there is an inappropriate increase in aldosterone synthesis in the setting of low plasma renin [6].

In addition to its main hemodynamic, fluid volume and vascular tone-changing effects, RAS can participate in stimulating immune cell infiltration, inflammation and fibrosis that is present in conditions such as renal ischemia, myocardial infarction and systemic hypertension [7]. Because of the connection of angiotensin II to endothelial dysfunction, proinflammatory and profibrotic actions and oxidative stress, it is associated with renal, cardiac and vascular injury and thereby directly linked to target organ damage in hypertension [7].

Besides the most largely known effector arm of the RAS, which includes angiotensin II and the angiotensin II type 1 receptor (AT1R), the RAS system is much more complex and features other important components, including angiotensin-(1–7) (Ang-(1–7)), which exerts opposite effects than angiotensin II—it leads to vasodilation, and it has antifibrotic and antiproliferative effects [8]. Angiotensin-(1–7) is being extensively studied, including for its potential antihypertensive effects. Its potentially favourable cardiovascular actions are elicited through Mas G protein-coupled receptors that are expressed in various tissues essential to blood pressure regulation such as the brain, kidneys, blood vessels and heart [9]. However, the clinical potential and role of angiotensin-(1–7) in the pathophysiology and treatment is not yet clear because of a lack of adequate clinical studies and data [9].

From a therapeutic standpoint, there are several important groups of pharmacological agents targeting the RAS in hypertension. These include already clinically well-established antihypertensive drugs such as inhibitors of the angiotensin-converting enzyme (ACE inhibitors), AT1R blockers or direct renin inhibitors [2]. However, novel potential drugs targeting the RAS are also being developed, including agents seeking to upregulate the ACE2/angiotensin-(1–7)/Mas axis—counteracting the unwanted actions of the ACE/angiotensin II/AT1R axis—or agents such as new small molecule inhibitors, recombinant ACE2 protein, as well as gene therapy suppressing angiotensinogen at the RNA level [2].

3. Role in heart failure

3.1 Introduction

Heart failure is a progressive condition defined by the inability of the heart to pump enough blood to meet the body requirements for nutrients and oxygen.

It develops when the heart fails to pump enough blood to meet the requirements of metabolizing tissues, which is caused by conditions like ischaemic heart disease, arrhythmias, etc., and produces different symptoms and signs. Some of the symptoms and signs include the following: exertional dyspnoea and/or dyspnoea at rest, orthopnoea, acute pulmonary oedema, chest pain, tachycardia, fatigue and weakness, distention of neck veins, rales, wheezing, S gallop or pulsus alternans, etc. [7].

Heart failure is one of the most challenging pathophysiologic states with increasing prevalence in the Western world, affecting 1–2% of the total population [10].

The neurohumoral basis of heart failure is complex and includes interaction between components of the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system and counterregulatory mediators (i.e., the natriuretic peptides).

Activation of neurohumoral mechanisms (i.e., the renin-angiotensin-aldosterone system) initially improves cardiac output, but despite this, counterregulatory mechanisms finally lead to heart failure syndrome with different signs and symptoms [11].

3.1.1 The neurohumoral pathophysiology of heart failure

The renin-angiotensin-aldosterone system (RAAS) plays a major role in the pathogenesis of heart failure, and the impact of treatment that targets RAAS is significant.

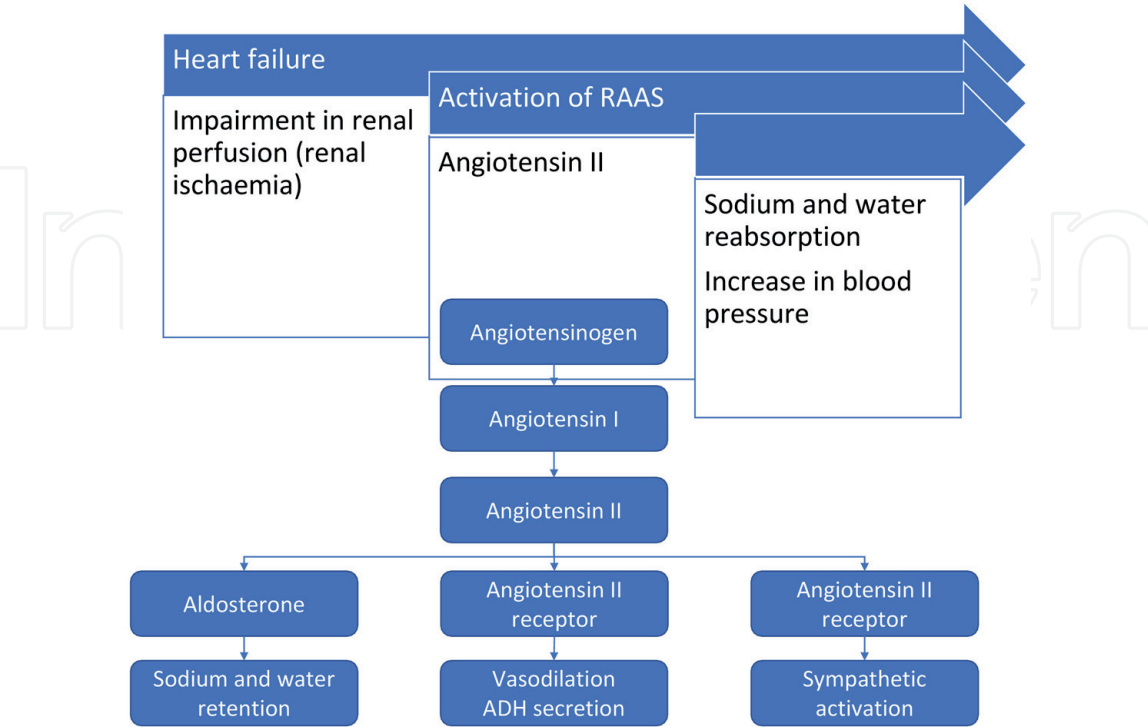


Figure 1.
A summary of the key pathogenesis of RAAS in heart failure. RAAS, renin-angiotensin-aldosterone system; ADH, antidiuretic hormone.

The neurohumoral basis of heart failure includes activation of RAAS by renal hypoperfusion (caused by hypotension or hypovolemia) and sympathetic activation [12].

Production of angiotensin II leads to vasoconstriction of arterioles and an increase in blood pressure, leads to antidiuretic hormone secretion, and stimulates the release of aldosterone and consequently salt and water retention [12] (**Figure 1**).

All of the above temporarily improve cardiac output but finally propagate the heart failure syndrome via overwhelming the opposing vasodilators and natriuretic mediators (i.e., A-type natriuretic peptide and B-type natriuretic peptide) which are mainly secreted from heart in response to the degree of ventricular stretch [13].

An imbalance between regulatory and counterregulatory mechanisms is the major pathophysiological target in heart failure treatment.

Therefore drugs that modulate RAAS (i.e., ACE inhibitors, beta-blockers, angiotensin receptor blockers and mineralocorticoid receptor antagonists) represent the core of treatment augmented by angiotensin receptor neprilysin inhibitors as a novel therapy [14].

4. Role in kidney failure

Chronic kidney disease (CKD) is a disease whose prevalence is constantly increasing in the elderly in the current, modern age [15]. CKD has multiple causes, where different organ dysfunctions lead to the reduction of the glomerular filtration rate, a disorder of excretory and endocrine function of the kidney and a significant diminishment of quality of life of such patients [16, 17]. End-stage renal failure, where glomerular filtration rate falls to less than 15 ml/min, requires treating the patient suffering from CKD with haemodialysis, which is a process in which blood is filtered through a semipermeable membrane, intended to replace the excretory function of the kidney [18]. Considering the high costs of treatment of patients with CKD, much research has been dedicated to studying the pathophysiological mechanisms that contribute to its development and exacerbation with the intention of developing new medications and procedures in an attempt to slow down the increase in the prevalence of patients with CKD. Abnormal activity of the renin-angiotensin system (RAS), regardless of the primary cause of CKD, has an immense value in the results of many studies [19].

In patients with CKD, RAS activity is increased in the central and peripheral circulation, which is indirectly confirmed by the fact that the activity and expression of the angiotensin-converting enzyme (ACE) linearly increases as the glomerular filtration rate decreases in patients with CKD [20]. Although ACE is the main enzyme that leads to RAS activation in patients with CKD by converting angiotensin I (Ang I) into angiotensin II, certain studies have shown that in particular types of acute renal failure, such as the one caused by aristolochic acid, there is a more significant RAS activation through chymases and a relatively mild ACE activation [21]. Chymase inhibition causes the slowing of the progression of fibrotic and inflammatory changes in the renal parenchyma, which makes it possible to talk about the synergistic effect of ACE and chymases in the activation of RAS effectors [21]. The role of chymase is also crucial for RAS activation in patients with stage five CKD treated with haemodialysis [22]. Considering the lower-than-normal levels of ACE and high chymase levels in such patients than those in patients with the same stage of CKD who are undergoing conservative treatment, it is clear that in such patients, the high levels of angiotensin in the renal parenchyma are a consequence of the increased chymase activity [22]. Increased chymase and angiotensin II activity leads to faster development of renal fibrosis

in patients treated with haemodialysis than that in patients with the same stage of CKD who are not treated with dialysis [22].

According to new findings, nearly all RAS components may have a big effect on the development of CKD and its predisposing factors, such as hypertension. The activity of the prorenin receptors (PRR), which is found in the collecting duct cells of the kidney and increases the affinity of renin for angiotensinogen, is significant for RAS activation [23]. PRR blockade in animal models causes the decrease of RAS activity, which indirectly decreases levels of proteinuria, macroscopic signs of interstitial fibrosis and renal fibrosis. Although the increased activity of the systemic RAS plays a large role in the development of CKD, new findings place greater emphasis on the role of the local RAS in the renal and brain parenchyma and their synergistic effects. Prolonged activation of the local RAS in the renal parenchyma causes the production of inflammatory cytokines IL-6 and TNF- α , which lead to the infiltration of inflammatory cells into renal tissue, tissue damage and fibrosis [24] (**Table 1**).

Recent studies have identified the Wnt/ β catenin signalling pathway as the main pathway for expression of RAS components in renal tissue, and its blockade in animal models of CKD was connected to significant clinical improvement and reduction of proteinuria and creatininaemia [25]. The Wnt/ β catenin signalling pathway is the main pathway for RAS expression in the hypothalamic paraventricular nucleus which indirectly affects the renal tissue RAS through activation of the sympathetic nervous system [26]. Blocking the central Wnt/ β catenin signalling pathway leads to the inhibition of expression of the renal RAS components and to the slowing of the progression of renal fibrosis; it is thus clear that in the tissue, local RAS is regulated by the central nervous system [5, 26]. Inhibition of RAS through intraventricular injection of losartan leads to a decrease in peripheral sympathetic nervous system activity and renal RAS activity, which potentially makes the sympathetic nervous system one of the possible pathways of communication between renal RAS and brain RAS [5]. In animal models of CKD, where a strong expression of RAS components was noticed after incubation of renal cells with inhibitors of the Wnt/ β catenin signalling pathway, there is mainly a reduced expression of profibrotic factors in the renal parenchyma. In one such model, positive feedback was noticed between RAS and the Wnt/ β catenin signalling pathway, where angiotensin II increases the expression of proteins of that signalling pathway, which is probably also the mechanism used by the central and circulating RAS to stimulate the activity of local RAS [25].

The role of the Wnt/ β catenin signalling pathway in RAS activation and local fibrosis is also confirmed by research done on its inhibitors. The Klotho gene, which plays a significant role in slowing the process of ageing, encodes the protein which inhibits the components of the Wnt/ β catenin signalling pathway [27]. In renal tissue of animal models of CKD, the Klotho level is inversely associated with the levels of RAS components, and the Klotho expression level showed a negative correlation with the degree of renal fibrosis [27]. Experimental studies on animal models that proved the effect of vitamin D on the decreased level of CKD and renal fibrosis measure an increased Klotho level, decreased activation of the Wnt/ β catenin signalling pathway and low tissue RAS activity in in vitro conditions [28]. Multiple experimental studies have demonstrated the connection between the Wnt/ β catenin signalling pathway and harmful RAS activation in CKD and renal fibrosis, which paves the way for new research with the aim of finding efficient medications that would slow the development and progression of CKD by affecting the above components [24, 26].

Local renal RAS may be activated by the effects of free radicals, which stimulate the expression of RAS components at the molecular level of signalling pathways. The above factor is one of the main mechanisms examined in harmful RAS

Component of RAS system whose activation or inhibition is involved in the development of CKD	Explanation of mechanism	References (author, year and title of study)
Prorenin receptor placed in collecting duct cells of kidney	PRR increases the affinity of prorenin and renin for angiotensin, and blockade of this receptor decreases activity of components of RAS and reduces laboratory markers of CKD	[23] (Fang et al., 2018, Role of (pro)renin receptor in albumin overload-induced nephropathy in rats)
Wnt/ β catenin signalling pathway as the main pathway for expression of RAS components in kidney and brain tissue (hypothalamic paraventricular nucleus)	Wnt/ β catenin signalling pathway is the main pathway of molecular expression of RAS components in brain and kidney tissue; local brain RAS and renal RAS communicate through the sympathetic nervous system	[26] (Zhou et al., 2019, The regulation effect of WNT-RAS signalling in hypothalamic paraventricular nucleus on renal fibrosis) [25] (Xiao et al., 2019, Wnt/ β -catenin regulates blood pressure and kidney injury in rats)
Angiotensin-converting enzyme in systemic circulation	Activity of ACE in systemic circulation increases with an increase of severity of CKD and in that way leads to further deterioration of kidney function	[20] (Wolke et al., 2017, Serum protease activity in chronic kidney disease patients: The GANI_MED renal cohort)
Chymase enzyme as an alternative pathway of activation of angiotensin II	Chymase, as an alternative pathway of RAS activation, converts angiotensin I to angiotensin II; blockade of this enzyme prevents CKD progression	[21] (Hsieh et al., 2017, Renal chymase-dependent pathway for angiotensin II formation mediated acute kidney injury in a mouse model of aristolochic acid I-induced acute nephropathy)
Neprilysin as an secondary enzymatic pathway for activation of angiotensin-(1–7)	Neprilysin, similar to ACE2 enzyme, converts angiotensin II to angiotensin-(1–7) which binds to Mas receptors and causes vasodilatory and renoprotective effects; prevents CKD	[31] (Domenig et al., 2016, Neprilysin is a mediator of alternative renin-angiotensin-system activation in the murine and human kidney)
Angiotensin receptor-associated protein (ATRAP), which is associated with AT1 receptor	ATRAP inhibits expression of AT1 receptor with circulating angiotensin II; it disables RAS activity in the development and progression of CKD	[32] (Kobayashi et al., 2017, An angiotensin II type 1 receptor binding molecule has a critical role in hypertension in a chronic kidney disease model)

Table 1.
RAS in the pathophysiology of renal failure.

activation in diabetic nephropathy, which is one of the leading causes of CKD [5]. The effect of free radicals on the development of CKD was demonstrated in studies examining strong antioxidants, such as melatonin. The application of melatonin in animal models of CKD leads to a reduced expression of all RAS components, decreased levels of markers of interstitial fibrosis and increased expression of antioxidant enzymes, such as superoxide dismutase [29]. The role of RAS in CKD has also been examined at the level of angiotensin receptors. Angiotensin II mainly produces its effect by activating the AT1 receptor, through which it causes vasoconstriction and has a proinflammatory and profibrotic effect on renal parenchyma. In addition to the AT1 receptor, there is also the AT2 receptor, which is presumed to have a vasodilatory and renoprotective effect. In experiments on animal models of CKD using resveratrol, which is a selective AT1 receptor antagonist and AT2 receptor agonist, increased expression of antioxidant

enzymes was demonstrated, as was a reduced expression of fibronectin and type IV collagen—which are markers of tissue fibrosis [30].

A similar role, but with another agonist as the AT₂ receptor, is played by the Mas receptor, which is also a part of RAS that contributes to local vasodilatation and has renoprotective effects. It is also known that, in normal circumstances, the Mas receptor is activated by angiotensin-(1–7), which is synthesized by the action of angiotensin-converting enzyme 2 (ACE2) on angiotensin II [31]. More recent studies of animal models with ACE2 enzyme blocking have determined the existence of stable levels of angiotensin-(1–7), and neprilysin was found to be the secondary enzymatic pathway contributing to its increase [31].

The AT₁ receptor activity is regulated by a special associated protein, which regulates its expression and thus indirectly also regulates RAS activity. ATRAP inhibits the expression of the AT₁ receptor and thus decreases the effect that circulating angiotensin II has on blood pressure levels, while also having a long-term effect by inhibiting the secretion of TNF- α , whose inflammatory factors contribute to the development of CKD [32].

The results of the latest studies confirm the essential role that RAS plays in the development and progression of CKD, which emphasizes the need and paves the way for new research on the subject of medications and therapeutic procedures that could efficiently decrease the growing epidemic of patients with CKD by affecting RAS components [32].

5. Role in diabetes

The RAS has been implicated in the human pathophysiology of numerous diseases, of particular importance in the development and onset of complications of diabetes as one of the most lethal non-communicable metabolic diseases [33]. The major intracellular mechanisms responsible for the adverse effects of diabetes are excessive production of advanced glycation end-products (AGEs), activation of the hexosamine biosynthetic pathway, activation of protein kinase C (PKC), lipotoxicity, mitochondrial dysfunction, enhanced oxidative stress and activation of intracellular RAS [34]. Because of hyperglycaemia in diabetes, intracellular accumulation of glucose that is not oxidised by glycolysis (because of inhibition of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) by reactive oxygen species (ROS)) is already being diverted to other metabolic pathways [34]. The result of GAPDH inhibition is the increased flux of glucose metabolites through four other metabolic pathways. These are the aldose reductase or polyol pathway, the formation of advanced glycation end-products, the formation of diacylglycerol (DAG), resulting in protein kinase C activation and increased flux via the hexosamine biosynthesis pathway (HBP), and generation of the end product uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), a substrate used for protein glycosylation [35]. The polyol pathway leads to NADPH and glutathione deficiency resulting in massive ROS formation [34]. On the other hand, in addition to leading to the development of insulin resistance, hyperlipidaemia also has a lipotoxic effect on cells [34]. Excessive fatty acid (FFA) inflow leads to increased and inefficient oxidation of FFA in the mitochondria with consequent generation of reactive oxygen radicals and exacerbation of mitochondrial dysfunction [34]. In diabetes, mitochondrial function decreases, and mitochondrial mass decreases, which is most likely connected to a decrease in OxPhos protein expression [34]. Excessive amounts of ROS, AGEs, DAG and activated PKCs and post-translational O-GlcNAcylation of transcription factors jointly lead to activation of intracellular synthesis of AGT, renin and chymase and thus activation of intracellular RAS. In addition, AGEs act

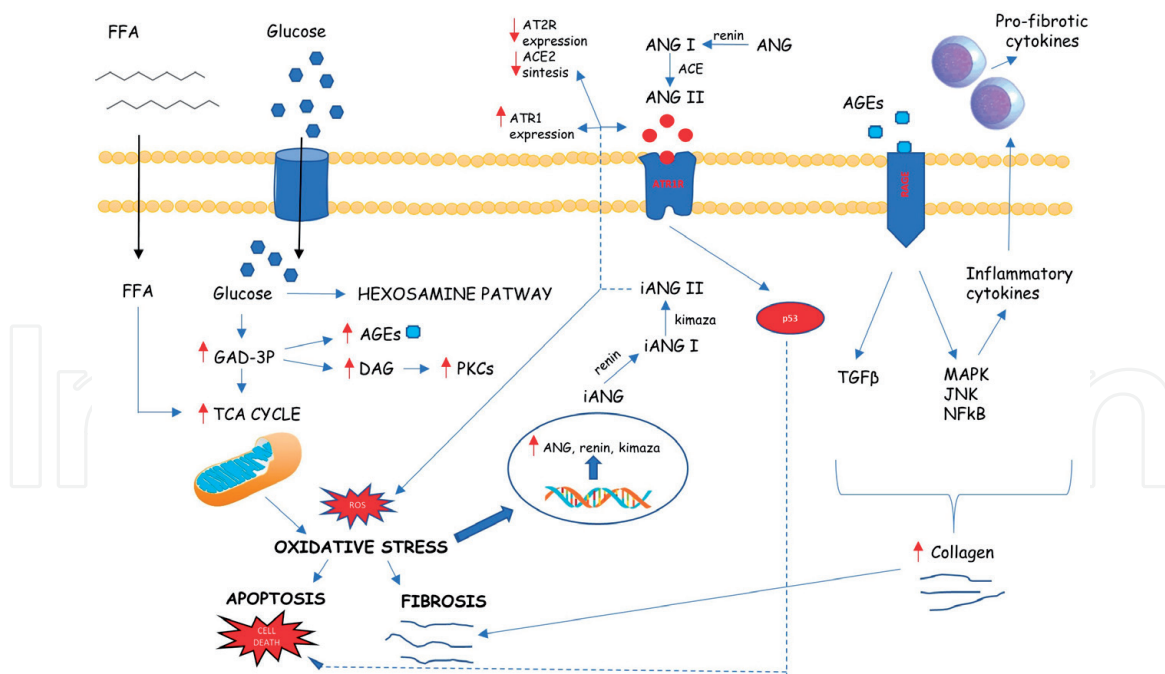


Figure 2.

Intracellular mechanism of activation and deleterious action of RAS in diabetes. ACE, angiotensin-converting enzyme; AGEs, advanced glycation end-products; Ang, angiotensinogen; Ang I, angiotensin I; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AT1R, angiotensin II type 1 receptor; AT2R, angiotensin II type 2 receptor; DAG, diacylglycerol; FFA, free fatty acid; GAD-3P, glyceraldehyde 3-phosphate; iAng, intracellular angiotensin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa beta; PKC, protein kinase C; RAGE, receptor for advanced glycation end-products; TCA cycle, tricarboxylic acid cycle; TGF-β, transforming growth factor beta.

via RAGE receptors that, through activation of inflammatory signalling pathways (TGF β, MAPK, JNK and NF-κB), lead to enhanced expression of collagen proteins and other extracellular matrix proteins. Together with activated RAS and activated PKCs isoforms by DAGs and by some lipid intermediates (e.g., ceramide, diacylglycerol and acylcarnitine), there is increased inflammation, fibrosis and apoptosis of cells attacked by hyperglycaemia [34] (**Figure 2**).

6. The role of intracellular Ang II (iAngII)

In addition to the commonly known circulating RAS, there is a local tissue intracellular RAS that occurs in all cells that produce peptides [36]. Activation of the transcription factors and gene expression described in the previous paragraph results in the synthesis of intracellular angiotensinogen, which is converted to angiotensin I by renin, and becomes the intracellular angiotensin II by the proteolytic action of chymase [34]. Chymase is a key proteolytic enzyme that completely replaces the role of extracellular angiotensin-converting enzyme within the cell and, unlike other alternative enzymes (tonin and cathepsin), has the highest substrate specificity. Intracellular Ang II levels are three times higher in diabetic patients than those in nondiabetic patients [37]. Intracellular Ang II has intracrine, autocrine, paracrine and endocrine functions [38]. iAngII by direct unidentified mechanisms, independent of global circulating RAS, causes an increase in oxidative stress and cell apoptosis and enhances the expression of intracellular components of RAS. Activation of AT1R via iAng II can trigger the MAPK signalling pathway (p38-MAPK), promoting inflammation, cell proliferation and thrombosis [37]. The study showed that an increase in phosphorylated p53 was associated with an increase in iAngII, enhanced activation of AT1R and RAS-independent O-glycosylation [39].

Also, iAng II enhances AT1R expression and decreases extracellular ACE2 expression in diabetic patients [37]. Increased expression of AT1R leads to stronger and negative effects of activation of AG1R [40]. ACE2 activation and AT2R activation are known to have protective effects on cells [38]. Direct inhibition, glycosylation or some other forms of protein modification leads to impaired ACE2 activity [41]. ACE2 catalyses the breakdown of Ang II to produce angiotensin-(1-7), which has an anti-inflammatory and antioxidant role [41]. In an animal model, it has been shown that oral administration of the recombinant-rich bacterium *Lactobacillus paracasei* (LP) can express and deliver human ACE2 to the circulation, which prevents the development of diabetic retinopathy and probably other forms of diabetes complication [41]. This potent protective effect of AT2R is prevented by the activation of AT1R by either iAngII or eAngII which results in the direct inhibition of AT2R activity or reduced expression of AT2R [38]. On the other hand, eAngII acts through AT1R and AG2R, and activation of a particular receptor depends on their balance regulated by the indicated intracellular mechanisms [38]. Thus, activation of AT1R by extracellular or intracellular Ang II leads to activation of several signalling pathways, activation of growth factor receptors, promotion of ROS synthesis and other apoptotic and fibrotic responses [37]. Patients with diabetes have 10 times higher levels of prorenin than renin than healthy subjects, and prorenin is thought to contribute more to the pathogenesis of diabetic complications [40]. Also, hyperglycaemia induces an increase in aldosterone by activation of AT1R and an increase in local Ang II whose pathophysiological effects in diabetes are unknown, but are thought to synergize with Ang II causing inflammation, apoptosis and fibrosis [42].

7. Influence of the RAS on pancreatic tissue, muscle tissue and adipose tissue

Chymase is found in all cells, and predominantly in mast cells, so we can also associate inflammation with the activation of RAS [43]. Activated intracellular RAS is thought to induce growth factor and cytokine synthesis by acting directly on other cells, which explains proteinuria in patients with diabetes with ACE inhibitors, resistance to antihypertensives in diabetics with hypertension and higher cardiovascular mortality in diabetics with hypertension [44]. Ang II reduces blood flow through beta Langerhans cells [45]. Ang II is thought to directly affect beta cell function and mass, promoting inflammation, oxidative stress and fibrosis [45]. All these effects finally lead to a decrease in insulin secretion and thus at least partially participate in the development of diabetes when it comes to beta cells [45]. Since muscle tissue accounts for about 80% of insulin-stimulated glucose disposal, the decrease in tissue perfusion caused by RAS directly contributes to the decreased glucose uptake into muscle cells [45]. On the other hand, it also leads to microvascular dysfunction, but all of this needs to be explored in more detail in the future [46]. Blockade of RAS causes overexpression of the GLUT4 transporter in skeletal muscle and accumulation of bradykinin that stimulates glucose uptake into skeletal muscle [47]. Long-term valsartan treatment reduced oxidative stress, NF- κ B activation and TNF- α expression in skeletal muscle [48]. iAngII synthesized in adipose tissue (AT) leads to adipocyte hypertrophy, increased lipid synthesis and storage and inhibition of lipolysis, thereby modulating the lipid capacity of adipocytes to develop and worsen insulin resistance [49]. Also, Ang II promotes AT gene expression by enhancing the synthesis of proinflammatory adipokines and thus macrophage infiltration [49]. In female mice lacking the angiotensin II type 2 receptor (AT2R), decreased insulin sensitivity to adipose tissue leads to compensatory adiponectinaemia [50]. Animal model research has shown

that RAS in diabetic rats leads to remodelling of the sympathetic nervous system, increased oxidative stress and increased norepinephrine levels in the myocardium itself [51]. In addition to its role in controlling electrolytes, blood pressure and vascular tone, RAS is involved in the development of inflammation, oxidative stress, metabolic syndrome, diabetes and its complications [49, 52–55].

8. Use of RAS inhibitors in patients with diabetes

Therapy with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) is a mainstay of treatment for diabetes mellitus (DM) because they prevent the development of diabetic complications [56]. Also, these drugs reduce the incidence of newly acquired DM II by 22% in the high-risk population by improving insulin sensitivity and insulin secretion [49]. Unfortunately, ARB and ACE inhibitors do not block iAngII, but only the autocrine and paracrine effects of extracellular Ang II, while the renin inhibitor aliskiren blocks extracellular and intracellular Ang II synthesis; therefore, aliskiren of all RAS inhibitors tested has the most potent effect in inhibiting fibrosis and apoptosis of cells exposed [49]. Insulin treatment showed no pronounced effect on the inhibition of iAngII synthesis [57]. Numerous meta-analyses state that many RAS blockers in use today will not have an additional benefit for diabetics over nondiabetics [38]. Today, attention is increasingly focused on the pharmacological activation of angiotensin II type 2 receptor and angiotensin-converting enzyme 2, which has been shown to reduce oxidative stress, inflammation, fibrosis and cell apoptosis in diabetics [57]. The protective effect has been demonstrated in combination therapy with activator neprilysin inhibitors (NEPi) with angiotensin-converting enzyme 2 [57]. This combination in diabetic rats significantly contributes to the inhibition of inflammatory, profibrotic and apoptotic signalling and thus prevents the development of diabetic cardiomyopathy and nephropathy [58]. Concomitant activation of the angiotensin II type 1 receptor (AT1) and activation of glucagon-like peptide-1 (GLP-1) receptor in insulin resistance leads to a decrease in oxidative damage to renal function and a significant decrease in albuminuria [59]. Urinary angiotensinogen may serve as an important marker of RAS activity, which may help in the decision to initiate treatment with RAS inhibitors and prevent the development and progression of complications in patients with diabetes [59, 60]. Numerous studies are based on uncontrolled studies of RAS inhibition; therefore, some studies discuss the beneficial effects on insulin sensitivity [61–65], and controversial studies report conflicting data [66–69]. Dosage and duration of treatment can be important factors that can create controversy, and in the future, they present us with a challenge in discovering the beneficial effects of inhibiting potent RAS [49].

9. Role in other clinical conditions

The local renin-angiotensin system in blood vessels of the brain parenchyma plays a significant role in regulating blood flow. The central nervous system RAS is separated from the systemic circulation by the blood-brain barrier, which enables the homeostasis of vasoconstriction and vasodilation of blood vessels in the brain, independent of blood pressure changes. Components of local RAS, such as renin, angiotensin II, ACE and AT1 receptor, participate in the cascade that results in vasoconstriction and anti-inflammatory effects, while activation of the AT2 receptor by angiotensin II and activation of the Mas receptor by angiotensin (1–7)

cause vasodilation and increase local brain tissue perfusion; the above has been demonstrated in experimental animal models [70]. Reduced levels of angiotensin-converting enzyme 2, which produces vasoprotective angiotensin (1–7), have been found in clinical trials of patients with acute ischemic stroke; its levels normalise only in the post-acute phase of the stroke [71, 72]. As regards the above, the most sensational research conducted is the research on experimental animal models in which a reduction in the size of the ischemic penumbra after a stroke was found upon the use of the AT1R antagonist and the AT2R agonist; this represents a new treatment option for patients with ischemic stroke [71, 73]. Apart from the effect it has on regulating cerebral circulation, RAS also has a great effect on learning and memory acquisition through the activation of the AT2 receptor within the hippocampus and the cortex [74]. In animal models of dementia induced by scopolamine, simultaneous oral treatment of mice with ACE and ARB inhibitors slows cognitive decline [75]. It has been confirmed in clinical trials that ACE inhibitors and ARBs have an effect on slowing the progression of dementia caused by Alzheimer's disease, cerebrovascular disease and other diseases [70].

Local RAS in the retina, which is also part of the central nervous system, plays a significant role in the development and progression of diabetic retinopathy. The effect of angiotensin II on the production of free radicals and inhibition of antioxidant enzymes, which causes an increase in VEGF production, which in turn leads to the development of diabetic retinopathy by stimulating angiogenesis, has been confirmed in experimental animal models [76].

RAS plays a significant, though as yet insufficiently explored, role in the regulation of physiological processes in the lung parenchyma, which is evident in the fact that long-term treatment by ACE inhibitors and ARBs decreases the incidence of inflammatory, infectious and structural diseases of the lung parenchyma [77].

Coronavirus disease 2019 (COVID-19) caused a serious pandemic, with cardiovascular disease (10.5%) having the highest mortality rate, especially if over 70 years of age [78]. The hypothesis of an association between the use of ACE inhibitors and COVID-19 is based on the fact that the COVID-19 agent (also known as SARS-CoV-2) uses the SARS-CoV receptor angiotensin-converting enzyme 2 for entry into target alveolar epithelial cells causing pneumonia [79]. ACE2 is found in endothelial cells, type I and II alveolar cells of the lungs, enterocytes, basal epidermal cells of the skin and epithelium of the nose, oral mucosa and nasopharynx, and ACE2 levels decline with age and are lower in patients with chronic diseases [80]. Cardiovascular patients taking ACE inhibitors or AT blockers significantly increase mRNA expression and activity of cardiac ACE2 [81]. By binding SARS-CoV-2, ACE2 is depleted, which inhibits the protective axis and may cause imbalances between the ACE/Ang II/AT1R pathway and the ACE2/Ang-(1–7)/Mas receptor in RAS, which may result in an increase in ACE activity and exacerbation of acute severe pneumonia by an increase in proinflammatory factors [82]. Animal models have also shown that acute ACE-induced lung injury results in increased ACE activity and Ang II expression, whereas ACE2 and Ang-(1–7) activities are reduced. In patients undergoing ACEi therapy, there is an increase in renin whose cascade response is directed towards the formation of ACE2 as an important balancing factor [83]. The binding of SARS-CoV-2 may decrease ACE2 function, leading to increased neutrophil infiltration into the lungs and resulting in excessive inflammation and injury [84]. The progression of inflammation could lead to hypoxia-induced enhanced expression of renin synthesis, which closes the vicious cycle, and it is clear that hypertension is an important risk factor in patients with COVID-19 [85, 86]. A meta-analysis conducted by Caldeira et al. did not highlight the protective effect of ACEi and ARBs [87]. A 5-year study showed that ACE administration had a higher risk of pneumonia than ARB administration. Low-dose lisinopril in neurological

dysphagia does not reduce pneumonia but increases mortality. Compared to calcium channel blockers, ACE inhibitors showed a lower mortality rate in patients with viral pneumonia [88]. Paradoxically, some authors report that chronic administration of ACE inhibitors or ARBs leads to an increase in ACE2 activity, which reduces the risk of infection because ACE2 dysregulation is triggered by the binding of a virus that increases the production of protective angiotensin-(1–7) [89]. This is based on the knowledge that ACEI/ARBs have shown an anti-inflammatory effect in the lungs, and it is suggested that they reduce the risk of pneumonia in elderly patients with hypertension with Parkinson's disease, in patients after CVI and in patients with chronic obstructive pulmonary disease (COPD) [90]. Patients with viral pneumonia who retained ACE and ARB had lower mortality rates and the need for intubation [91]. A major Chinese study has reported that ACE2 expression level is not crucial for the severity of COVID-19 infection but also plays an important role in the immune response and viral particle count and that, given pressure control, ACEi and ARBs can be used in patients with new types of coronavirus pneumonia to reduce pulmonary inflammation and reduce patient mortality rates [80]. No information is currently available on the number of hospitalized COVID-19 patients with hypotension, but it can be considered as an important limiting factor for the use of ACE inhibitors or ARBs in the treatment of COVID-19 patients [89]. Thus, we do not yet have the most accurate information on the real impact of ACEi and ARBs on infectious diseases such as pneumonia. Research should be conducted as soon as possible to prove the hypotheses and thus reduce the risk of mortality in patients taking ACE inhibitors and/or AT blockers.

At its molecular level, vitamin D is a prorenin molecule transcription antagonist. In animal models with knockout genes for vitamin D receptors, this is reflected in an elevated transcription of renin-angiotensin system components, development of hypertension and chronic cardiac and renal failure [92]. Data obtained through clinical studies that investigated possible therapeutic uses of vitamin D supplementations on RAS was inconsistent. Exogenous application of vitamin D has a distinct effect on local kidney tissue RAS. It causes a reduction in angiotensin excretion in patients with chronic renal failure and/or in renal transplant recipients [93, 94]. However, in prospective studies, the simultaneous application of vitamin D and drugs that affect RAS on patients with arterial hypertension or in normotensive patients did not result in a decrease in arterial pressure or the difference in RAS component concentrations [95, 96]. The exception with regard to the previous statements is the prospective study carried out by Wu et al., in which a decrease in blood pressure values was noted after 6 months of perioral administration of high doses of vitamin D, as well as a decrease in atherosclerotic plaque circumference and thickness on epicardial blood vessels of test subjects that underwent a coronaryography [97]. The latest data points out an evident need for supplementary studies that must include a sufficient period for observation and a sufficiently large dose of vitamin D supplementations that would achieve a clearly notable effect on the observed variables.

Ghrelin, which is a peptide hormone secreted by the stomach, fulfils its physiological role by binding to target receptors in the central nervous system in which it triggers the feeling of hunger or the need for sleep by regulating hormone levels [98]. However, according to newly acquired data, the acylated form of this enzyme plays a significant, opposite role in the cardiovascular system, namely, in the area of the heart ventricle and aorta. Unlike RAS, which causes ischemic expansion and tissue degradation in cases of acute myocardial infarction, ghrelin has an opposite effect that is realized through its receptors. It causes a reduction in angiotensin-converting and proapoptotic enzyme expression, along with a reduction in oxidative stress [99].

10. Therapy targeting the RAS

Knowledge of the physiology of RAS and participation in the pathophysiology of cardiovascular and other diseases has led to the development of drugs that have an effect on numerous stages of the synthesis of RAS components and their action on known RAS receptors. Blocking of RAS is achieved by direct inhibitors of the enzyme responsible for the synthesis of RAS component (renin-angiotensin-converting enzyme) and inhibition of receptors through which they exert their effects (angiotensin receptor blockers) [100]. In recent years, new RAAS components have been discovered whose pathways have protective effects, which have enabled the development of new therapeutic targets [101]. One of the most impressive approaches in the study of novel therapeutic methods is the selective deletion of hepatic angiotensinogen [102].

10.1 Direct renin inhibitors

A low molecular weight non-peptide renin inhibitor that is well tolerated and has clinical utility is called aliskiren [103]. Clinical trials have demonstrated a strong antihypertensive and organoprotective (cardioprotective, renoprotective) role for the renin inhibitor [104, 105]. It has been shown to be very good at regulating blood pressure in hyperthyroid rats [106]. The use of aliskiren showed a decrease in the antidiuretic effect of renin [107]. This drug has a potent antifibrotic activity mediated by the reduction of oxidative stress and fibrogenic cytokines in all tissues [108].

10.2 ACE inhibitors

ACE is a multifunctional enzyme with numerous biological substrates. These classic drugs directly inhibit the vasoconstrictive and proliferative effects of the already known ACE/Ang II/AT1R axis and indirectly stimulate the production of the vasoprotective and antiproliferative peptide Ang-(1–7) [100].

10.3 Angiotensin I receptor antagonists/blockers (ARBs)

Selective AT1 receptor blockers inhibit the effects of Ang II on AT1R. The main effect is the inhibition of vasoconstriction, i.e., the reduction of peripheral vascular resistance, without significantly affecting the heart rate [109]. Administration of these drugs significantly reduces cardiovascular mortality, stroke, myocardial infarction and the onset and development of complications of diabetes [110]. The consequence of AT1R blockade is an increase in the secretion of renin, ACE and consequently Ang II [109].

10.4 Other therapeutic compounds

10.4.1 β 1 blockers

Blocking the sympathetic β 1 receptor in plasma cells of the dense macula results in a decrease in plasma renin levels. An effect on the reduction of Ang II has been demonstrated. β 1 blockers also reduce the conversion of prorenin to renin [111].

10.4.2 Prorenin receptor antagonist/blocker

The newly discovered prorenin receptor blocker is a decoy peptide for the handle region of the prorenin average (HRP) [112]. It binds competitively to the non-proteolytic domain of prorenin, thereby preventing its activation [113].

Studies have shown that its administration reduces renal and cardiac impairment without affecting blood glucose levels in diabetic and antihypertensive rats [112]. Transgenic rat models with overexpression of the prorenin receptor showed massive proteinuria and glomerulosclerosis, but administration of HRP significantly suppressed the production of proteinuria and glomerulosclerosis, but without affecting the level of circulating Ang II [114]. Another study questions the use of HRP in which there was no reduction in target organ damage in hypertensive rats, nor did the blockade affect the expression of the prorenin receptor. It is thought that HRP cannot block extracellular signal-regulated kinases (ERKs) that induce prorenin and renin and that its positive effect depends on an undefined mechanism and not on the antagonism of the prorenin receptor. Clearly, this receptor plays a major role in the human body, but its cellular biology and its impact on the cardiovascular system need further investigation [112].

10.4.3 Chymase inhibitors

The chymase enzyme is only active in damaged tissues resulting from the activation of intracellular RAS [115]. The chymase can convert TGF-beta and MMP-9 precursors into their active forms that induce inflammation and fibrosis. To date, there are no specific results from human studies, but animal models have shown that inhibitors of chymase enzyme prevent vascular proliferation, myocardial fibrosis after cardiac infarction, development of diabetic complications, development of skin keloid and the occurrence of abdominal aortic aneurysm [116].

10.4.4 Angiotensin II receptor agonist

The first synthesized oral agonist was called Compound 21 (C21), which showed organoprotective, anti-inflammatory, antithrombotic, antifibrotic and antiapoptotic effects in an animal model. It has a very high affinity for AT2R and a low affinity for AT1R [103]. C21 lowers mean arterial pressure and improves ventricular function after myocardial infarction [117]. It significantly stimulates the growth of the hippocampal neurons, and its role mediated through AT2R in enhancing congenital functions is further investigated [118].

10.4.5 Activation angiotensin-converting enzyme 2 and Mas receptor agonist

Activation of the protective axis of RAS by ACE2, Ang-(1-7) and Mas receptors achieves beneficial vascular effects. The aim of this therapeutic target is to enhance the effect of ACE2, reduce the level of circulating Ang II and redirect the formation of Ang-(1-7), which by acting on AT2R and Mas receptors, achieves its protective effect. For the time being, the administration of human recombinant ACE2 is known to have an antihypertensive effect. ACE2 diminazene aceturate (DIZE) activator also reduces body weight and markers of adipogenesis and improves plasma lipid profile. They have a protective and pancreatic effect because it increases proliferation and decreases β -cell apoptosis and promotes glucose-stimulated insulin secretion. Overexpression or expression of ACE2 enhances basal and insulin-stimulated glucose uptake into cells, especially hepatocytes and adipocytes. Another tested ACE2 activator is 1-[[2-(dimethylamino) ethyl] amino]-4-(hydroxymethyl)-7-[[4-(methylphenyl) sulfonyl] oxy]-9H-xanthone-9 (XNT), which, through 2 weeks of continuous treatment, led to an improvement in endothelial function in hypertensive and diabetic rats by reducing oxidative stress. It also causes Mas receptor-mediated vasodilation [119]. In diabetic rats, it reduced pulmonary hypertension and significantly improved function and

reduced myocardial fibrosis [120]. Therefore, in addition to the antihypertensive effect, the use of ACE2 activator leads to beneficial metabolic effects that reduce the possibility of diabetes and its complications [119]. Deficiency of Mas receptor genes or blockade of Mas receptors in male mice results in a metabolic syndrome that includes hyperlipidaemia, hyperglycaemia, hyperinsulinaemia, increased insulin resistance, increased glucose intolerance and adiposity [121]. The use of Mas agonists AVE0991 in animal models showed mild cardioprotective effects and an effect on lowering glucose and lipid levels in the blood [122]. Another Mas agonist of hydroxypropyl- β -cyclodextrin (HP β CD), in addition to increasing the half-life of Ang-(1–7), reduced the adverse effects and magnitude of myocardial infarction, myocardial hypertrophy and isoproterenol-induced heart damage. The remaining two agonists CGEM856 and CGEM857 cause vasodilation and cardioprotection [123]. In addition to Mas receptors, there are probably other receptors through which Ang-(1–7) exerts its effects, but this needs to be revealed in the future [119]. Virus-mediated ACE2 gene expression, i.e., gene therapy, has shown cardioprotective and antihypertensive effects in animal models. ACE2 overexpression by gene therapy is not limited to the heart but shows effects in brain and lung tissue where it exhibits antihypertensive effects [123].

10.4.6 Analogue of Ang-(1–7)

Although it is a very attractive therapeutic target, there are very limited studies today because of the short lifespan of this hormone. The clinical studies conducted focused on the intra-arterial or intravenous administration of infusions of the Ang-(1–7) analogue, which exerts its immediate vasodilatory effects. ACE inhibitors and angiotensin receptor antagonists, by their action, indirectly redirect the metabolic pathway of RAS towards the formation of increased levels of Ang-(1–7) [124].

10.4.7 Vaccines

The Ang I vaccine showed no antihypertensive effect, probably due to low antibody levels. Ang II vaccine, on the other hand, has proven to be very effective with a half-life of about 4 months. It was formed by covalent attachment of virus-like particles derived from the bacteriophage Q β envelope and modified Ang II. The antihypertensive effect manifested on systolic and diastolic pressures mostly in the early morning hours compared to placebo [125]. In addition to preclinical, it has also been tested in clinical trials with mild side effects such as flu symptoms. The more recent divalent vaccine HBcAg-CE12-CQ10 has shown antihypertensive and renoprotective properties without immune or electrophysiological adverse effects and has specific binding to AT1R and L-type calcium channels [126].

10.4.8 Alamandine

Recently, a new member of the RAS family named alamandine was discovered on animal models. It acts on MrgD receptors and exerts vasodilatory and cardioprotective effects similar to Ang-(1–7) [127]. Deletion of the MrgD gene at an early age resulted in the development of gender-independent dilated cardiomyopathy [128]. Endogenous alamandine is known to reduce leptin synthesis and secretion by activating the c-Src/p38 MAP kinase pathways, which is contrary to the action of Ang-(1–7) [129]. To date, no studies have been conducted on the administration of drugs that modulate this newly discovered component of RAS, so there is an opportunity to discover new therapeutic strategies in the future [127].

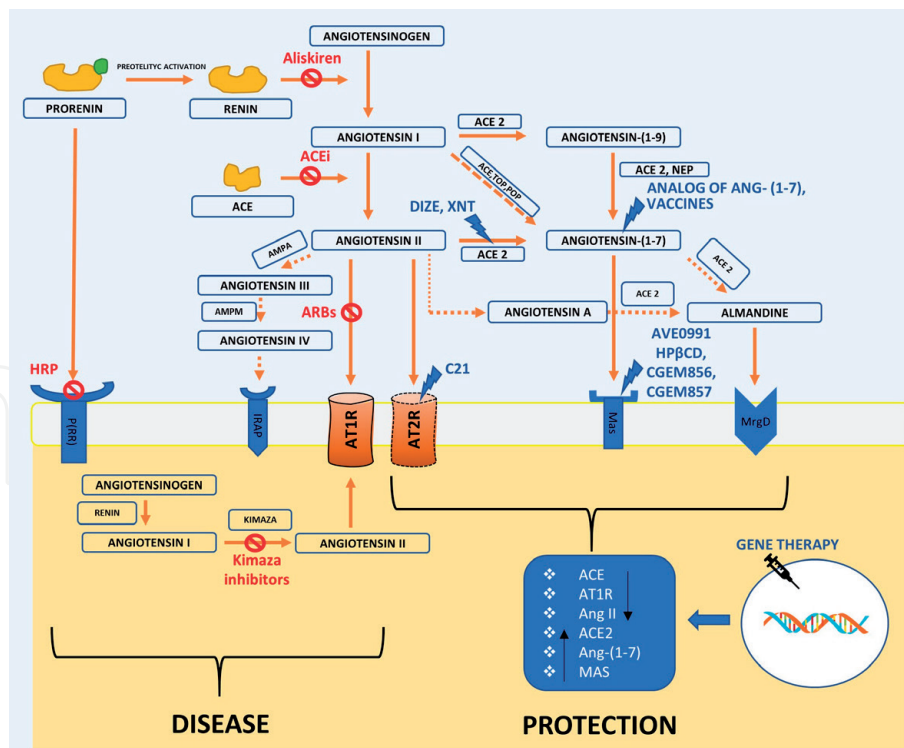


Figure 3. *Influence of specific therapeutic strategies on components of the RAS. ACE, angiotensin-converting enzyme; AMPA, aminopeptidase A; AMPM, aminopeptidase M; Ang, angiotensin; ARBs, angiotensin receptor blockers; AT1R, angiotensin II type 1 receptor; AT2R, angiotensin II type 2 receptor; AVE0991, orally active Mas receptor agonist; C21, Compound 21 (AT2R agonist); CGEM856 and CGEM857, orally active Mas receptor agonists; DIZE, ACE2 activator diminazene aceturate; HPβCD, Mas agonist hydroxypropyl- β -cyclodextrin; HRP, decoy peptide for handle region of the prorenin prosegment; IRAP, insulin-regulated aminopeptidase receptor; MasR, angiotensin-(1–7) Mas receptor; MrgD, Mas-related G protein-coupled receptor; NEP, neprilysin; POP, prolyl oligopeptidase; PRR, prorenin receptor; TOP, thimet oligopeptidase; XNT, ACE2 activator xanthenone.*

10.5 Perspectives

The use of RAS-A blockers to date has not been shown to be sufficient to achieve the desired effects on the cardiovascular system [130]. With the realization that there is a protective axis within RAS, pharmacotherapy and gene therapy are increasingly focused on the activation of the protective components of RAS. The greatest challenge in the future remains to unravel the mutual mechanisms of regulation of the vasoconstrictive and vasoprotective axis. It is important to explore whether the expression of one enzyme/receptor induces the expression or inhibition of another, which are the mechanisms of action of the protective axis at the cellular level, which are the consequences of prolonged activation or inhibition of RAS, whether we can act more selectively on RAS and are there additional undetected roles and consequences of deleterious action therapies on RAS. We also need to further investigate the impact of gender, organ function, dosage and timing of administration on the targeted effect of therapy [123]. Discoveries and the complex modulation of RAS add a great challenge to the treatment of the most common diseases of humanity [130] (**Figure 3**).

Conflicts of interest

The authors have no conflict of interest to declare.

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