Review

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Angiotensin-Converting Enzyme 2 and its Potential in the Respiratory and Cardiovascular Systems

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Angiotensin-converting enzyme 2 (ACE2) is a zinc metallopeptidase that participates in the metabolism of renin-angiotensin system (RAS) hormones and serves as the entry point for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. This review explores the characteristics of ACE2 as a potential therapeutic target for various conditions, including acute respiratory distress syndrome, pulmonary fibrosis, pulmonary hypertension, atherosclerosis, myocardial infarction, arterial hypertension, and arrhythmias. The literature highlights that angiotensin II (Ang II), a very active hormone in the RAS, exacerbates these conditions through pro-inflammatory, pro-fibrotic, and oxidative stress-inducing effects. Oxidative stress and immune system overactivation are critical factors in the progression of cardiovascular and pulmonary diseases. Ang II is synthesized by ACE and is subsequently converted to angiotensin-(1-7) (Ang-(1-7)) by ACE2, which counter regulates the effects of Ang II. ACE2's importance is observed during SARS-CoV-2 infection, where its association with the spike protein leads to decreased ACE2 levels, increased inflammation and reactive oxygen species, thereby worsening the diseases selected for this review. In conclusion, ACE2 can be a potential therapeutic target due to its ability to mitigate the harmful effects of Ang II, offering potential benefits in the treatment and prevention of different diseases.

Keywords: angiotensin II; angiotensin-converting enzyme 2; angiotensin-(1-7); SARS-CoV-2; lung; cardiovascular system

Introduction

Renin-angiotensin system (RAS) is an endocrine system composed of various enzymes and products. A series of biochemical reactions in this system synthesize different hormones involved in maintaining the body's homeostasis. The primary functions of the RAS include regulation of blood pressure, inflammatory responses and coagulation reactions [1]. The entire series of reactions in the RAS begins with the cleavage of angiotensinogen (AGT). The main enzymes involved in the RAS are renin, angiotensin-converting enzyme (ACE), and angiotensin-converting enzyme 2 (ACE2), as shown in Fig. 1. Renin, which is produced in juxtaglomerular cells, starts the chain of reactions by converting angiotensinogen to angiotensin I (Ang I). This biologically inactive peptide is then transformed into angiotensin II, the hormone with the highest activity in the RAS [2]. The reaction is catalyzed by ACE, which removes two amino acids from Ang I. ACE is present in the cells of the liver, kidneys, intestines, and blood vessels, in both incorporated and soluble forms. Angiotensin II (Ang II), an ACE product, fulfills its role by interacting with the angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R). Binding to the first receptor results in vasoconstriction, blood clotting, inflammatory response, increase in blood pressure, matrix remodeling and profibrotic response [1,3]. Additionally, it promotes the synthesis of aldosterone and vasopressin which stimulate sodium and water reabsorption, as well as potassium secretion in the kidneys. Interaction with the AT2R receptor causes effects opposite to those mentioned above. ACE2 is the third most important enzyme in RAS. ACE2 mediates the cleavage of Ang II, resulting in the production of angiotensin-(1-7) (Ang-(1-7)). The effects of Ang-(1-7) depend on binding to the MAS receptor (MasR). Interaction with this receptor causes effects opposite to those caused by Ang II. In addition to the aforementioned enzymes, neprilysin and chymase also participate in the RAS by converting different forms of angiotensin [3,4]. The overall effect of the RAS depends on a balance between its homologous enzymes. An imbalance in these enzymes can lead to various abnormal conditions [1]. In addition to the functions mentioned above, the RAS plays a critical role in the regulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Ang II activity promotes increased ROS production. An imbalance between their production and neutralization causes oxidative stress, linked to chronic diseases like pulmonary and cardiovascular disorders [5].

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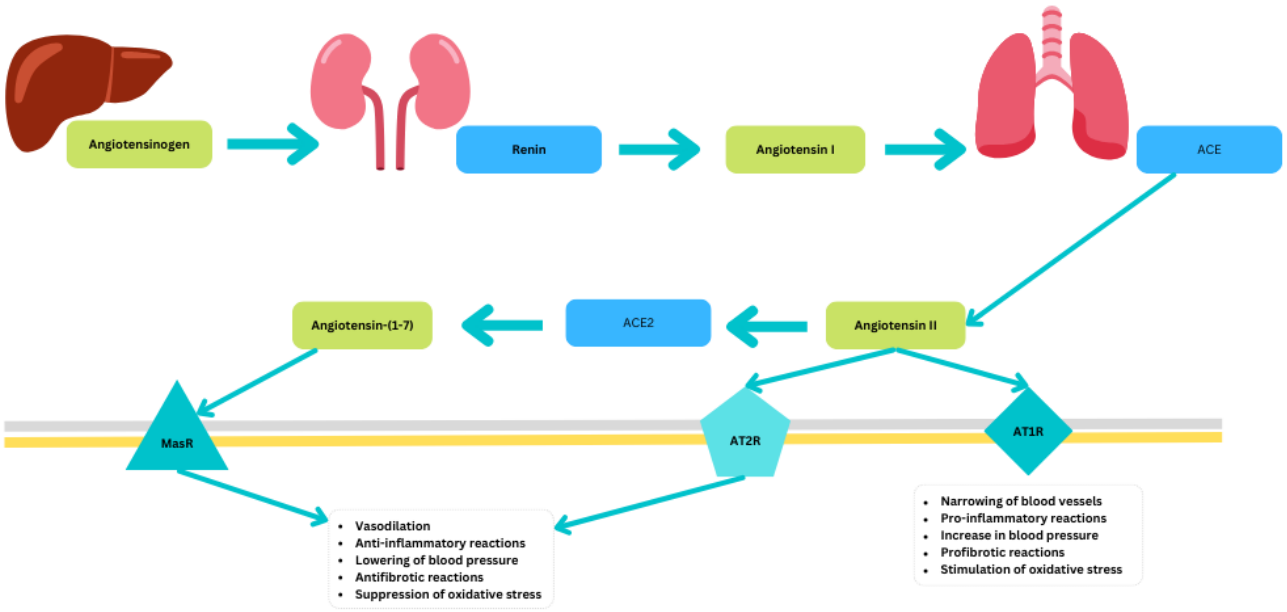

Fig. 1. Renin-angiotensin system (RAS)/angiotensin-converting enzyme 2 (ACE2). This figure illustrates the cascade of enzymes and hormones in the RAS, highlighting some of the most important components and transformations. The process starts with angiotensinogen in the liver which is converted by renin, ACE and ACE2 into active peptides such as angiotensin II (Ang II) and Ang-(1-7). This diagram shows some of the properties of these hormones in interaction with the respective receptor. The diagram was created using Canva (https://www.lifeatcanva.com/en/locations/australia/, Liver and Kidney illustration: ©sparklestroke via canva.com, Lung illustration: ©Twemoji via canva.com). AT1R, angiotensin II type 1 receptor; AT2R, angiotensin II type 2 receptor; MasR, MAS receptor; Ang-(1-7), angiotensin-(1-7).

Characteristics of ACE2

The protein was discovered in 2000 by two independent groups of researchers. The enzyme is 40% identical and 61% similar to its counterpart, ACE [6]. Comprising 805 amino acids, ACE2 belongs to the zinc metallopeptidase enzymes [7]. The gene responsible for the synthesis of the enzyme is located on the X chromosome, specifically in the Xp22.2 region. ACE2 exists in two forms: primarily incorporated in cell membranes and in smaller amounts dissolved in body fluids like blood and urine [7]. It is found in various tissues and organs including the brain, lungs, heart, liver, small intestine, kidneys, thyroid, testes, adipose tissue, colon, adrenal glands, blood, bone marrow, spleen, muscles and blood vessels [8]. The occurrence of ACE2 in these organs is confirmed by the presence of mRNA encoding this protein in the relevant tissues [9]. ACE2 consists of an N domain and a C domain. The C domain, which plays a role in binding the protein to the membrane, consists of 22 amino acids, while the N signaling domain consists of 17 amino acids. The amino acid sequence forming the conserved motif contains glutamine at position 402, which serves as a ligand for zinc. The presence of zinc in the Histidine-Glutamate-X-X-Histidine (HEXXH) sequence classifies ACE2 as a metalloproteinase [10]. ACE2, as a mono-carboxypeptidase is involved in degradation of various peptides, such as angiotensin's, opioids, kinins and apelins [6]. ACE2 is a key receptor for both Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), facilitating the entry of these viruses into cell [11].

ACE2 and ARDS

The lungs are among the organs that contain ACE2. This enzyme contributes to balanced functioning of the RAS, and it may also be a potential target in the treatment of certain airway diseases. Most of the ACE2 in lungs is found in type I and II alveolar cells with smaller amounts in bronchial epithelial cells and endothelium, as well as in arterial smooth muscles [12]. ACE2's role in the RAS, as well its action against Ang II, may provide beneficial effects in the treatment of some airway abnormalities, such as acute respiratory distress syndrome (ARDS), a severe form of acute lung injury (ALI) leading to lung damage and decreased tissue oxygen concentration. ARDS is characterized by fluid leakage into the lungs through their vascular system, causing an exaggerated inflammatory response, increased tissue mass, and restriction of the large surface area of this organ for gas exchange [13]. RAS is an important factor affecting the progression of ARDS. Ang II interaction with the AT1R receptor induces pro-inflammatory, vasoconstrictive and profibrotic action, mak-

ing this hormone a driving factor in ARDS. This is supported by a study in which the induction of pulmonary fibrosis (PF) by injection of lipopolysaccharide (LPS) caused increased levels of Ang II and AT1R in plasma [14]. One of the key points in controlling ARDS is the immune system. The ACE2/Ang-(1-7)/MasR axis counteracts the effects of Ang II by reducing the level of inflammatory response. Ang-(1-7) minimizes the synthesis of the pro-inflammatory such as cytokines tumor necrosis factor alfa (TNF-α) and interleukin-6 (IL-6), and increases the synthesis of the anti-inflammatory cytokines interleukin-4 (IL-4) and interleukin-10 (IL-10) [15,16]. It also prevents macrophage polarization by decreasing the expression of Toll-Like Receptor 4 (TLR4) receptors and normalizing the Nuclear Factor Kappa-B (NF-κB) and Mitogen-Activated Protein Kinase (MAPK) pathways [15]. ACE2 decreases Ang II levels, reducing its pathophysiological actions, including inflammation. ACE2 additionally reduces the synthesis of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α [17]. ACE2 is present in small amounts on the membranes of certain immune cells, such as macrophages and T lymphocytes [18]. SARS-CoV-2 disrupts the balance of T lymphocytes and increases their activity, indicating that ACE2 is a key element in the modulation of T lymphocytes [19]. This fact implies that ACE2 is involved in reducing the activity of T lymphocytes. Study shows that macrophages are infected by the SARS virus, further demonstrating the presence of ACE2 in these cells [20]. Deficiency of the ACE2 enzyme causes several negative effects on the respiratory system, including hyperresponsiveness of the immune system [21]. Increased infiltration of cells that form the defense system, including macrophages, demonstrates the inhibitory role of the enzyme. These findings underscore the potential of ACE2-based therapies in treating ARDS and highlight the need for further clinical trials to validate these promising results.

ACE2 and Pulmonary Fibrosis

PF is a disease characterized by changes in tissues building the alveoli, inflammation, accumulation of fibroblasts and their transformation into myofibroblasts, regulation of extracellular matrix production and oxidative stress. The main cells involved in fibrosis are fibroblasts, myofibroblasts and, mainly macrophages present in the alveoli [22]. Macrophages produce cytokines and profibrogenic factors in response to damage to alveolar epithelial cells and arterial epithelial tissue. Some of these factors include chemokine (C-C motif) ligand 1 (CCL1), Transforming Growth Factor-beta (TGF-β), and Growth Differentiation Factor 15 (GDF15) [23,24]. Immune cells, such as lymphocytes, macrophages and neutrophils produce ROS, activating of NF-κB and leading to an enhanced immune response [25,26]. Ang II plays a significant role in pulmonary fibrosis by promoting inflammation and fibrosis. In idiopathic pulmonary fibrosis (IPF), increased levels of AT1R, renin, AGT, and ACE receptors are observed [27]. Activation of AT1R by Ang II leads to the recruitment of immune cells and the release of proinflammatory cytokines. The inflammatory response involves macrophages that carry a quantity of AT1R and Ang II. Ang II also promotes ROS synthesis via NADPH oxidase 1 (NOX1), NOX2, and NOX4 activation [28]. ACE2 counterbalances the Ang II effects by converting it to Ang-(1-7), reducing profibrotic and proinflammatory actions. In lung injury, the presence of ACE2 is low, as shown by the amount of mRNA encoding the protein [29]. This phenomenon allows to increase the amount of Ang II and enhances the impact of the ACE/Ang II/AT1R chain. Increasing the amount of ACE2 can be done through the injection of recombinant human ACE2 (rhACE2) or the application of diminazene aceturate (DIZE). Increase and activation of this protein have shown positive effects by reducing the synthesis of collagen I, TGF-β1, proline and Alpha-Smooth Muscle Actin (α-SMA) [29]. Ang-(1-7) through its MasR, produces positive effects by preventing the development of pulmonary fibrosis. The presence of Mas receptors on alveolar cells, epithelium, airway smooth muscles, vascular smooth muscles, endothelium, as well as immune cells, such as alveolar macrophages, lymphocytes, eosinophils and neutrophils, gives Ang-(1-7) a wide field of action in terms of its positive effects [30]. Oral administration of Ang-(1-7) in mice with bleomycin-induced fibroses reduced ROS and inflammatory reactions [31]. Ang-(1-7) is classified as short lifespan in plasma, leading to experiments on increasing its activity by combinations with other elements, using analogs or MasR agonists [32].

ACE2 and Pulmonary Arterial Hypertension

Pulmonary hypertension is a disease associated with abnormal remodeling of the pulmonary arteries, the cause of which is right ventricular failure [33]. Increased Ang II activity associated with the AT1R exacerbates Pulmonary Arterial Pressure (PAP) and Pulmonary Vascular Resistance (PVR), which further causes the development of Pulmonary Arterial Hypertension (PAH) [34]. A crucial role in PAH plays the immune system, with immune cells like macrophages, dendritic cells, mast cells and B, T lymphocytes accumulating in the perivascular area. Apart from these cells, there are also cytokines, such as IL-1β, IL-6 and IL-18, as well as inflammatory mediators, chemokines and the complement system [35]. The activity of the immune system in arteries damages the endothelium and stimulates the proliferation of arterial smooth muscle cells [36]. Reactive oxygen and nitrogen also play roles in the development of PAH. Imbalance in these molecules caused by various factors leads to oxidative stress, endothelial dysfunction and an increase in the synthesis of contractile factors such as endothelin-1 [37]. Oxidative stress activates p38 mitogen-activated protein kinase (p38MAPK), extra-

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cellular signal-regulated kinase 1 (ERK1), and c-Jun N-terminal Kinase (JNK) proteins, which cause vascular cell proliferation, as well as vascular cell hypertrophy and inflammation [38]. ACE2 contributes to the prevention of disease exacerbation. This fact is also confirmed by scientific studies motivated by the need to fully discover its significance in patients with PAH. Such an experiment was conducted by Shen *et al*. [39]. This group of researchers used Mouse Double Minute 2 homolog (MDM2) to block AMPK, which in combination with ACE2, increases its stability. This phenomenon resulted in an increase in pro-PH factors [39]. In another experiment conducted on human cell cultures, ACE2/Ang1-7/MasR induced vasodilation. This phenomenon was caused by a series of reactions, such as inhibition of ERK1/2 and proto-oncogene tyrosine-protein kinase Src (c-Src) phosphorylation, as well as reduction of ROS synthesis and stimulation of nitric oxide (NO) synthesis [40]. NO, prostacyclin, and endothelin (ET) are critical in PAH development. Prostacyclin, released by endothelial cells, relaxes pulmonary smooth muscles and inhibits their proliferation by releasing cyclic adenosine monophosphate (cAMP) [41]. Ang-(1-7), through stimulation of Mas receptors, causes a release of Arachidonic Acid (AA), which is an essential precursor for prostacyclin synthesis [40]. Another element that plays a role in the development of PAH is ET. The effects caused by ET-1 binding to the ET_A receptor promote vasoconstriction, proliferation and enhancing the inflammatory response [42]. ACE2 reduces ET-1 synthesis by catalyzing Ang II and inhibiting sympathetic ventricular neurons, which is considered to have a stimulatory effect on the RAS ability to increase Ang II levels [43]. Ang-(1-7) activates endothelial NOS (eNOS) through the Akt kinase signaling pathway, promoting NO synthesis [40]. NO dilates pulmonary vessels by activating a series of reactions, starting with the activation of soluble guanylate cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP). This product further activates protein kinase G I (PKG I), which has a vasodilatory effect [44]. The presence of the molecule Considering the positive effects of ACE2, there has been increased interest in using this protein for therapeutic purposes. Some ways to increase its blood concentration include the use of ACE2 activators, recombinant ACE2, gene transfer by lentiviruses or adenoviruses, and DNA microparticle transfer. Research studies are still being conducted to find a stable way of exploring the potential of protein in diseases of the respiratory system.

ACE2 and the Cardiovascular System

RAS is an important factor in the cardiovascular system responsible for maintaining homeostasis of blood pressure. In heart, ACE is present in cardiomyocytes, cardiac fibroblasts and the endocardium. This enzyme also occurs in blood vessels found throughout the body [28]. There are two main enzymes in the synthesis of cardiac Ang II and chymase, with chymase playing the major role [45]. In the cardiovascular system, AT1Rs are present both in the heart and in all blood vessels [46]. In the cardiovascular system, ACE2 appears in endothelial cells and smooth muscles, as well as in cardiomyocytes, fibroblasts and pericytes [40]. The G-protein-coupled receptor (MAS) in this system is found in cardiomyocytes, fibroblasts and endothelial cells [47].

ACE2 and Atherosclerosis

Atherosclerosis is a cardiovascular condition caused by accumulation of lipids and an inflammatory process in arteries. The factors that lead to the development of atherosclerosis are inflammation in the cardiovascular system, lipid accumulation and damage to the endothelial layer [48]. Interaction of Ang II with the AT1R receptor, causes the activation of calmodulin, an increase calcium concentration in endothelial cells, and activation of NOX [49]. The synthesis of ROS leads to the activation of NF-κB factor, which plays an important role in initiating the inflammatory response. Together with Ang II, NF-κB induces the production of several essential factors for the immune response including cytokines (TNF-α and IL-6), chemokines (Monocyte Chemoattractant Protein-1 (MCP-1)), and P-selectins, which include adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), macrophage colony-stimulating factor (M-CSF), and cyclooxygenase-2 (COX-2) [49,50]. This activation results in inflammation and recruitment of immune cells in the vascular endothelium. Macrophages, derived from monocytes, deposit Low-Density Lipoprotein (LDL) and transform it into foam cells which are accumulated in the subendothelial layer [51]. The involvement of T lymphocytes leads to a progressive inflammatory response and synthesis of other ROS molecules. Apart from NF-κB activation, reactive oxygen species also cause migration of smooth muscle cells and collagen deposition. The whole chain of reactions results in the formation of atherosclerotic plaques [52]. The activity of Ang II enables VSMC migration and proliferation through activation of ERK 1/2, p38 MAPK and c-JNK [53]. Ang II also increases NO oxidation, reducing NO levels, which is manifested as endothelial malfunction and reduced dilation. The activity of Ang II is limited by the ACE2 enzyme and its antagonist Ang-(1-7). Activation of NOX is a significant phenomenon in the onset and development of atherosclerosis as the products of the enzyme are related not only to vascular inflammation, but also to lipoprotein modification [54]. Oxidative stress reduction by ACE2 depends on the reduction of Ang II and the synthesis of Ang-(1-7). Reduction of reactive oxygen species produces positive effects, including inhibition of the production of pro-inflammatory factors, such as cytokines and

chemokines. One of the ways to reduce NOX activity is the preventive action of Ang-(1-7) on ERK 1/2 MAPK and c-Src protein activation [55]. In an *in vivo* study, the Ang-(1-7)/MasR axis was shown to balance the occurrence of TLR4 receptors in macrophages, which prevents the development of inflammatory response through the NF-κB and MAPK activation pathways [15]. Chemokines and selectins involved in the development of atherosclerosis are also influenced by Ang-(1-7) since, through its action, the synthesis of MCP-1, VCAM-1 and E-selectins is reduced [49,56]. Ang-(1-7) also increases the amount of NO production, a very important element in maintaining vascular homeostasis. The Ang-(1-7)/MasR interaction leads to activation of the Phosphoinositide 3-Kinase (PI3K)/Protein Kinase B (Akt) chain, which triggers phosphorylation of endothelial NO and thus increases the amount of this molecule in the free state [49]. The activity of ACE2 has gained interest among many researchers as a factor involved in the prevention or treatment of atherosclerosis. Efforts to fully identify this enzyme are underway. Most experiments have been conducted on laboratory animals and cell lines. A deeper understanding of ACE2 may eventually lead to other strategies and options for reducing symptoms or managing atherosclerosis.

ACE2 and Myocardial Infarction

Myocardial infarction (MI) is another abnormality caused by loss of oxygen supply to various areas of the heart due to blockage of blood vessels. Lack of oxygen can result in dysfunction of the circulatory organ, which can lead to death. A promising method for assessing microscopic changes is biomarkers, such as creatine Kinase-MB (CK-MB), Heart-Type Fatty Acid Binding Protein (hFABP), N-Terminal pro B-Type Natriuretic Peptide (NT-proBNP), B-Type Natriuretic Peptide (BNP), TNF, IL, MPO, interleukin 1 receptor-like 1 (ST2), GDF15, or vascular endothelial growth factor receptor (VEGFR) [57]. Among the above biomarkers, various experiments show that ACE2 levels in patients after myocardial infarction are higher than those observed in healthy individuals [58,59]. An increase in the level of this enzyme can be useful in assessing cardiac changes after a heart attack, while at the same time, high levels of ACE2 can have a protective function against further complications that can lead to heart failure. After myocardial infarction, necrotic areas composed of dead cardiomyocytes begin repair and regeneration processes. Dead cells are gradually replaced by extracellular matrix (ECM). The main cells that produce ECM components, such as fibronectin and collagen, are fibroblasts. Another phenomenon in the repair process following myocardial infarction is hypertrophy of cardiomyocytes and involvement of immune cells. The influence of the above factors affects cardiac remodeling. Some experiments have shown that elimination of the *ACE2* gene resulted in an increased incidence of ventricular remodeling due to activation of some of the previously mentioned biomarkers, e.g., IL and TNF, or others, i.e., Matrix Metalloproteinases (MMPs), interferons which recruit immune cells and lead to myocardial fibrosis [58,60]. The product of ACE2, Ang-(1-7), also occurs in high concentrations after MI, and some studies show that this hormone has a protective effect on tissue remodeling [61,62]. A phenomenon observed after myocardial infarction is proliferation of cardiac fibroblasts. Results of *in vitro* research study demonstrates that when rhACE2 is applied, an antiproliferative effect occurs [63]. All patients who survive myocardial infarction can experience a number of complications that negatively affect the normal functioning of the heart. Knowledge of the activity of the ACE2/Ang-(1-7)/MasR axis in the myocardium allows us to prevent adverse consequences and maintain the physiological norms of the affected organ.

ACE2 and Arterial Hypertension

Hypertension is a disease that affects a large proportion of the world's population. Blood pressure means the force exerted by blood on the veins of the body. If it exceeds the normal values, an anomaly known as hypertension is diagnosed. Multiple factors contribute to arterial hypertension, many of which are related to the activity of RAS. The immune system, is a well-organized complex of cells, receptors and transmitters. Also contribute to the occurrence and development of pathological conditions, such as hypertension [64]. Ang II stimulates inflammation, negatively impacting hypertension by increasing vascular permeability, leukocyte infiltration and tissue remodeling [65]. Leukocyte infiltration is mediated by receptors located in the vascular endothelium. The receptors include selectins and immunoglobulin superfamilies [65]. E-selectins and P-selectins bind to the relevant receptors present in leukocytes, leading to their recruitment with Ang II increasing amount of these selectins [66]. Adhesion of leukocytes follows recruitment, facilitated by other molecules belonging to the immunoglobulin superfamily, ICAMs and VCAMs. Yin *et al*. [67] demonstrated that blocking of VCAM receptors resulted in an improvement in laboratory animals with hypertension induced by Ang II. ICAM-1 is also higher in cells treated with Ang II than in control cells [68]. Cytokines, IL-6, MCP-1, TGF-β, interferon-gamma (IFN-γ) and TNF-α are also involved in the pathogenesis of hypertension, stimulated by the pro-inflammatory activity of Ang II [69]. Besides the immune system, oxidative stress plays a significant role. Experimentally, oxidative stress stimulation stress by Buthionine sulfoximine (BSO) leads to complications related to hypertension [70]. Cytokines and hormones regulate the activity of enzymes involved in ROS synthesis. The amount of reactive oxygen species increases due to the stimulation of NOX, which depends on the interaction between Ang II and AT1R [71]. Oxidative

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stress causes vascular inflammation, endothelial dysfunction, NO reduction, sodium homeostasis regulation, and atherosclerosis, all promoting hypertension [72]. Endothelin is another crucial element involved in the pathogenesis of hypertension. Increased levels of ET-1 by Ang II, activate the immune system, inflammatory response, ROS production and NO reduction [73–75]. Apart from producing the above-mentioned effects, Ang II participates in increasing blood pressure owing to its vasoconstrictive properties and through activation of aldosterone which increases sodium and water absorption. In summary, Ang II activity causes blood vessel remodeling, increased constriction and endothelial dysfunction. A review of hypertension, namely pulmonary arterial hypertension indicates that one of the main causes of this condition is a group of factors that have a pathological effect on the arteries. Factors such as activity of the immune system, reactive oxygen species, reduction of NO, or increase in hormones such as endothelin, etc., promote the onset and development of hypertension. The aim of some research studies is to counteract the factors that stimulate hypertension through various mechanisms, such as receptor blockers, antagonism of mediators, etc. A very good option is the use of hormones that have the opposite effect to those that cause disease. In the case of hypertension, ACE2 is seen as a promising protein that can be used in the prevention of the condition, owing to its catalytic effect on Ang II, which, as mentioned above, has prohypertensive properties. Additionally, ACE2 is a key element in the formation of Ang-(1-7). Combining the ACE2/Ang1-7/MasR chain with positive effects, analyzed in the paragraph on pulmonary arterial hypertension, may offer a potential solution for prevention and treatment of hypertension in the future.

ACE2 and Cardiac Arrhythmia

Cardiac arrhythmia is characterized by an irregular heartbeat resulting from a serious dysfunction of the elements that respond to the transmission of the impulse that causes heart muscle to contract and release. Several factors are involved in the pathogenesis of cardiac arrhythmias including reactive oxygen species. Increased ROS production plays a key role in the development of various diseases, including cardiac arrythmias [76]. Various studies show that reactive oxygen species affect the function of ion pumps, which are crucial for maintaining the heart's rhythm. Avula *et al*. [76] show that mitochondrial-derived ROS creates a direct current from Na^+ ions, leading to arrhythmia. Another study found that the use of H_2O_2 induced a delayed Na^+ current (laterNa) which is a continuous flow of sodium ions through ion complexes along the action potential (AP) plateau [77]. Calmodulin (CaM) is a protein that binds to various ion complexes. This combination allows the regulation of ion transport. Calmodulin a protein that regulates ion transport binds to the Ryanodine Receptor 2 (RyR2), a protein that forms a Ca^+ ion transport channel from the sarcoplasmic reticulum. Uncontrolled ROS levels negatively impact this chain, inducing cardiac arrhythmias by electrophysiological changes [78]. Immune system also contributes to arrhythmia. Interleukins, particularly IL-17 play a crucial role in the pathogenesis of arrhythmias. IL-17 stimulates other pro-inflammatory cytokines, such as IL-1β, TGF-β and IL-6, and disrupts calcium ion homeostasis [79]. This phenomenon was verified by Tsai *et al*. [80] in a research study on rabbits, where the presence of IL-17 caused ventricular arrhythmias. IL-18 also activates NF-κB and is also involved in cardiac arrhythmias [81]. Immune cells particularly macrophages have pro-arrhythmic properties. They induce pro-inflammatory effects, cause ionic disturbances and remodeling of gap junctions [82]. Moreover, the KCa3.1 protein in macrophages can also cause arrhythmia as demonstrated by a study in which the KCa3.1 channels were blocked, and this resulted in inhibition of atrial fibrillation [83]. Fibrosis, particularly vascular fibrosis induced by the effect of Ang II and AT1R, is another factor in cardiac arrhythmias. Ang II-induced fibrosis occurs in blood vessels and contributes to several conditions such as atrial fibrillation (AF) and hypertension [84]. In all the aforementioned factors, such as reactive oxygen species, the immune system and cardiac fibrosis, Ang II is a stimulatory agent. The main role of ACE2 is to reduce the amount of the hormone and synthesize Ang-(1-7), thus producing the opposite effect to that of Ang II. As previous study has shown, Ang-(1-7), through its binding to MasR, activates the transcription of genes responsible for crucial proteins including a subunit of the Kv4.3 potassium channel and a subunit of the alpha 1E calcium channel that regulates electrical activity and cardiac rhythm [84]. The ACE2/Ang-(1-7)/MasR chain is a promising agent which may alleviate cardiac arrhythmias by regulating electrical activity, reducing the inflammatory response and preventing fibrosis. This chain may be a powerful element in the prevention or mitigation of arrhythmias.

Impact of SARS-CoV-2 on Respiratory and Cardiovascular Diseases

In 2019, a new pathogen began to threaten the world, becoming the cause of the coronavirus disease 2019 (COVID19) pandemic. On 11 March 2020, the World Health Organization (WHO) declared COVID19 a global pandemic disease. According to WHO statistics, by 8 November 2023, the number of confirmed cases of coronavirus infection was 771,820,937, with a mortality rate of 6,978,175. The main route of SARS-CoV-2 transmission is inhalation of aerosols. As illustrated in Fig. 2 the key agent in infecting the cells of the body is ACE2. This protein serves as a receptor for this type of virus. The organs most affected by this infection are the lungs. Ashraf *et al*. [85] reported that coronavirus can also affect the tongue,

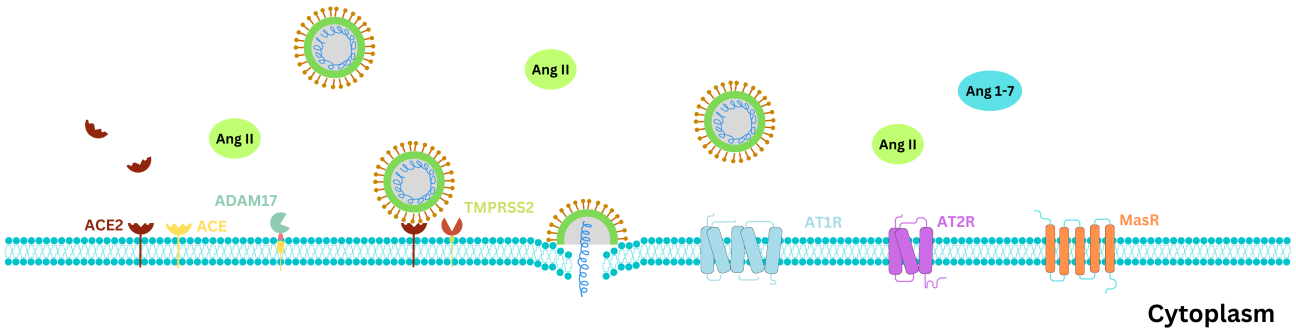

Fig. 2. Cell infection by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This figure illustrates the interaction of SARS-CoV-2 with the RAS system. The component that enables the virus to enter the cell is ACE2 in cooperation with the TMPRSS2 enzyme. In this illustration, other elements of the RAS system are presented, such as ACE, Ang II and Ang-(1-7) as well as the respective receptors. Also illustrated is A disintegrin and metalloproteinase 17 (ADAM17), which enables the cleavage of the extracellular domain of ACE2. Created using Canva (https://www.lifeatcanva.com/en/locations/australia/, Liver and Kidney illustration: ©sparklestroke via canva.com, Lung illustration: ©Twemoji via canva.com).

mouth, vascular system, heart, gastrointestinal tract, kidneys, pancreas and brain. When lung cells are infected, various parts of the lung become damaged, promoting fibrosis due to factors with reparative properties. A very important element contributing to the occurrence of pulmonary fibrosis is macrophages. Wendisch *et al.* [86] described the role of SARS-CoV-2 in macrophages based on the results of an *in vivo* experiment. It revealed that the virus causes not only transformation of monocytes into profibrotic macrophages, but also induction of chemokines and proteinases, such as CCL2, CCL8, CCL24, MMP9, MMP14 and others, which also affect the development of pulmonary fibrosis. In a research analysis, Xu *et al.* [87] describe how SARS-CoV-2 interacts with several proteins, such as ACE2, TGF-β and CTGF, which promotes extracellular matrix synthesis, resulting in profibrotic effects. COVID19 patients are also affected by the cytokine storm. This fact was revealed by Harrison *et al.* [88] who explain that high amounts of cytokines and chemokines, such as IFN-I, IFN-II, TNF-α, IL-1B, IL-6, IL-8, IL-18, granulocyte-macrophage colony-stimulating factor (GM-CSF), C-X-C motif chemokine ligand 9 (CXCL9), CCL-2, CCL-3, CCL-4, result in lung damage. People infected with SARS-CoV-2 confront another phenomenon, i.e. higher activity of NADPH oxidase, which increases the amount of reactive oxygen species [89]. Based on the findings presented in the previous sections of this paper, it has been shown that factors contributing to pulmonary hypertension include immune system activity and reactive oxygen species. This information is important when determining the effect of SARS-CoV-2 infection on pulmonary hypertension. To verify this fact, Tudoran and his co-researchers observed potential complications following COVID19, one of which was pulmonary hypertension [90]. A research study on concomitant diseases affecting individuals infected with this virus found that some of these patients had atrial fibrillation, a type of arrhythmia [91]. The presence of the ACE2 receptor in endothelial cells makes the latter a target for the SARS-CoV-2 virus. ACE2 binding by the coronavirus favors the demonstration of Ang II effects. Damage to arterial endothelial tissue, stimulation of inflammation, increase in reactive oxygen species and Ang II, as well as lipid accumulation are all typical causes of atherosclerosis [92]. The above factors, involved in the development of atherosclerosis, may also be responsible for the occurrence and progression of arrhythmias [93]. The analysis clearly shows that coronavirus is not limited to alveolar tissue damage. The consequences of infection with the virus can also be seen in other parts of the body, which are affected by various complications. A very important element mentioned in this article is the negative reactions that occur because of a decrease in ACE2 protein. This phenomenon is an excellent example that illustrates the positive role the enzyme plays in the body. Since ACE2 is the key to the infection of cells by SARS-CoV-2, various studies are experimenting with the use of this protein to prevent infection by the virus. Regdanvimab (CT-P59) is a monoclonal antibody that shows efficacy in preventing spike protein-ACE2 interaction. CT-P59 binds to the receptor binding domain (RBD) in ACE2, which results in covering the binding surface of the virus. Clinical trials show that regdanvimab has brought about a reduction in viral infection and consequently a decrease in hospitalization of patients with mild and moderate infection [94]. In addition to monoclonal antibodies, researchers have paid attention to natural compounds derived from plant extracts. Salvinorin A and deacetylgedunin are two molecules that have shown high inhibitory properties against spike-ACE2 binding. *In vitro* studies have shown that these compounds block the infection of cells by the virus. They also have low cytotoxicity, which makes them safe for use [95]. ACE2 is a very important protein in the human body. Its presence in various tissues balances the effects caused by Ang II. Infection by SARS-CoV-2 significantly decreases the amount of this enzyme, leading to complications such as ARDS [96]. The

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use of ACE2 blockers is also a challenge for researchers, as they aim to ensure that the activity of this protein is not adversely affected. Given the presence of ACE2 in different tissues, we also understand the impact that SARS-CoV-2 has on the body. Effective infection management and prevention of COVID-19 are key to preventing various diseases resulting from RAS imbalance. Understanding the role of ACE2 in physiological balance provides essential insights into the development of effective treatments.

Angiotensin Converting Enzyme 2: A Promising Therapeutic Agent

Due to its regulatory role against the RAS, ACE2 is seen as a potential therapeutic for several diseases. A therapeutic intervention of recombinant ACE2 (rACE2) against coronavirus has demonstrated a beneficial effect, prompting interest in its potential applications for other medical conditions. In studies involving rats with lung injury, administration of rACE2 caused a reduction of edema, inflammation, oxidative stress and normalization of angiotensin levels. Decreased levels of pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and the enzyme myeloperoxidase, as well as a reduction in the oxidative stress marker 8-Oxoguanine glycosylase (OGG1) evidenced this fact [97]. Another method of enhancing ACE2 activity is by using activators. One such activator is DIZE, antiparasitic drug that activates ACE2. This activation has been associated with various beneficial outcomes, including blood pressure reduction, cardioprotection, renoprotection, and anti-inflammatory effects. Additionally, one of the significant positive effects of ACE2 activation is the inhibition of tumor growth and metastasis, highlighting the potential of this protein as an anti-cancer agent [98]. Antioxidant, anti-inflammatory effects and improvement of renal function were observed during an experiment where Xanthenone, an ACE2 activating substance, was applied to mice with nephrotoxicity [99]. One of the experimental methods involves delivering the *ACE2* coding gene using various vectors. Specifically, the mACE2-rAAV2/8 vector facilitates the production of the *ACE2* gene in the liver. This approach has been shown to decrease Ang II levels in the liver, reduce biliary fibrosis, and enhance antifibrotic activity [100]. *ACE2* gene therapy thus presents a promising potential treatment for pulmonary fibrosis and other related diseases. The therapeutic potential of ACE2 presents an opportunity for using this protein in different medical applications. However, like any therapeutic agent, ACE2 therapy comes with its own set of challenges. While it can have beneficial effects, it may cause physiological imbalances in other systems for ex. Immune system. One significant challenge is the delivery of ACE2. One significant challenge is the delivery of ACE2. Ensuring that the protein reaches its target in the body is crucial, as it may encounter various substances, particularly enzymes that can degrade it. For gene therapy is a challenge to find a safe and appropriate viral vectors. *ACE2* gene therapy introduces additional complexities, such as the risk of gene overexpression. It is essential to secure the introduced genes to avoid the mutations. Most ACE2 therapy experiments have been conducted on laboratory animals. In some cases, protein may not elicit the same response in humans as it does in animal models. Another challenge is individual variability in response to ACE2, which could result an ineffective therapy or causing adverse effects in some individuals. However, the therapeutic properties of ACE2 hold great promise. Therefore, studies should continue in order to avoid challenges and increase efficiency in the treatment of people.

Conclusions

Some of the diseases in which RAS affects their progression were mentioned above. The immune system and reactive oxygen and nitrogen species have a significant impact on these diseases. Disturbance of the balance of ROS and RNS causes oxidative stress, which in turn supports the inflammatory response. The immune system, while trying to protect the body, sometimes transitions into a pathological state. These two systems are influenced by the effects of Ang II. Ang II often causes deterioration in pathological conditions in both the respiratory and cardiovascular systems. Its properties manifest through its connection with AT1R, which triggers a cascade of reactions that stimulate the inflammatory response and the production of reactive species. The function of this hormone can be prevented or minimized by inhibitory or antagonistic substances that prevent binding to AT1R. Within the RAS, there is a natural element that counteracts the effects of Ang II. Ang-(1-7) exerts effects opposite to those of Ang II when it binds to MasR. ACE2, in addition to synthesizing Ang-(1-7), also decreases the amount of Ang II, thereby reducing its effects. ACE2 is seen as a therapeutic target for several diseases. Recombinant ACE2, ACE2 activators, application of the *ACE2* gene, and ACE modulators are some of the methods researchers use to study its effects. Some of the challenges researchers face include the duration of its activity, sustainability, safety, efficacy, and methods of application. As a protein, it began to gain popularity at the beginning of the SARS-CoV-2 pandemic. Consequently, experiments with this protein are limited, as are scientific articles. Future efforts to use ACE2 as a therapeutic will focus on its safety and efficacy. This protein could become crucial in the future for the relief and healing of certain diseases in the body.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the corresponding author if needed.

Author Contributions

ET, ME, MP and JS performed the research and wrote the original draft. ME, MP and JS designed the methodology and made the analysis. ET, ME, MP and JS made the data curation. ET, ME and MP made acquisition of data and edited the manuscript. ET perfomed the global analysis and edited the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Makandjou-Ola Eusebio and Miroslawa Pietruczuk are serving as the Editorial Board of this journal. We declare that Makandjou-Ola Eusebio and Miroslawa Pietruczuk had no involvement in the peer review of this article and have no access to information regarding its peer review.

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