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Review | Internal Medicine

Renin-Angiotensin System: A Review of Historical Perspectives

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Abstract
The article is a review of publications concerning historical perspectives of the renin-angiotensin system. The discovery of its components is presented in chronological order, beginning with the initial identification of renin and proceeding to the subsequent discoveries of angiotensin-converting enzyme 2, angiotensin-(1-7), Mas receptor.
This paper presents a modern classification of the renin-angiotensin system, dividing it into classical and non-classical branches, based on the determination of the biological effects of its components. Significant attention is devoted to elucidating the biochemical cascade of the renin-angiotensin system, its physiological transformations, and its implications in human body processes. The detrimental cardiac effects of the classical renin-angiotensin system are highlighted, along with the crucial role played by its alternative axis in counteracting the development of cardiovascular diseases.
The article presents data on the involvement of angiotensin-converting enzyme 2 and its receptors in coronavirus infections, susceptibility to infection, and disease progression.

Keywords
Renin-Angiotensin System; Angiotensin-Converting Enzyme 2; Angiotensin-(1–7); Mas Receptor

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Introduction

The renin-angiotensin system (RAS) plays a pivotal role in regulating essential physiological functions and maintaining homeostasis, particularly in the context of blood pressure regulation. The dysregulation of the RAS leads to the development of cardiovascular pathology [1–3]. Its components have been studied since the 19th century, with the subsequent discovery of new substances, their addition to the system, and exploring their biochemical, physiological, and pathophysiological effects. A significant scientific achievement was the determination of the role of renin, angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and its receptors in the pathogenesis of arterial hypertension and heart failure which led to a new direction of pharmacotherapy - the development of targeted drugs. This has made a great contribution to treatment tactics and is considered as an important strategy for the treatment of concomitant pathologies. The study of the RAS has evolved, leading to the discovery of new components, including ACE2, Ang-(1-7), Mas receptor [4–6]. Since the discovery of ACE2, tremendous advance has been made in elucidating its biochemical properties and fundamental importance in the pathogenesis of different diseases. In the current coronovirus infection, the importance of ACE2 as a receptor for severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has been proven and its dominant pathway in the pathophysiology of COVID-19 has been shown by influencing virus expression/transmission and clinical manifestations/complications [7].

The aim of the review is addressed to the historical stages of researching various axes of the RAS, with an emphasis on possible underlying mechanisms responsible for the development of chronic pathologies associated with the RAS. The review elucidates the relationship between the RAS and the SARS-CoV-2 virus, the causative agent of COVID 19, and identification of RAS-targeted clinical approach in such patients.

Discovering the Renin-Angiotensin System: Historical Landmarks

The RAS is a complex multifunctional network of enzymes, peptides, and receptors. The history of the discovery of the RAS began in 1898 in the laboratory of the Karolinska University in Stockholm, where Robert Adolf Arman Tigerstedt and Per Bergman worked on an experimental model of rabbits that underwent nephrectomy. They detected

an increase in blood pressure in animals after administering an extract obtained from the cortical layer of the kidney. This extract was referred to as renin [8] (Table 1).

In the 20th century, researchers continued to study renin due to the pressor effect it had on the body by narrowing the renal artery [9]. During experimental studies conducted in the late 1930s, Braun-Menéndez *et al.* (Argentina) and Page *et al.* (USA), in 1940, concluded that the pressor activity of renin was associated with its proteolytic action and the ability to convert the peptide present in plasma into a substance increasing blood pressure [10, 11]. Both Argentinian and American scientists independently discovered this peptide, and they named it "hypertensin" and "angiotonin", respectively. In collaborative research, the author team suggested "angiotensin" for the enzyme and "angiotensinogen" for its precursor.

The two types of angiotensin, Ang I and Ang II, were discovered in 1954 by Skeggs *et al.* [12]. In 1956, they found that ACE, which is a dipeptidyl carboxypeptidase, was involved in the production of Ang II. Ang II octapeptide is formed when ACE or chymase cleaves the dipeptide from the C-terminus of Ang I [13]. At a molecular level, human endothelial ACE, characterised as a 170-kDa glycoprotein containing two homologous active sites, was first cloned in 1988 by Soubrier *et al.* [14].

Ang II is converted into Ang III and Ang IV by various aminopeptidases. In 1980, the arterial concentration of Ang III was first recorded in sheep and accounted for 42% of that of Ang II [15]. In addition, it can be generated from Ang I by ACE [16]. Ang III can be converted into Ang IV by aminopeptidase N (APN) [17].

The effects of Ang I and Ang II were found to be mediated by specific cell surface. The two types of Ang II receptors – angiotensin type 1 receptors (AT_1 receptors) and angiotensin type 2 receptors (AT_2 receptors), have been identified pharmacologically and by expression cloning [18–20].

Recently, the classical view of the role of the RAS as an endocrine system has been revised. Further study of this system is associated with the discovery of novel RAS components going beyond the paradigm that is already known. New components of the RAS were first discovered in 1968, when Yang *et al.* demonstrated that pig kidneys and human urine contained angiotensinase, which destroyed polyphenylalanine of various peptides [5].

This hydrolysis resulted in the heptapeptide Des-phe-Angiotensin II, named Ang-(1-7), which was considered a new enzymatic pathway of angiotensin inactivation. In 1982, the ability of this enzyme to inactivate Ang I and Ang II was discovered, and in 1988, applying immunohistochemical techniques, its localization in the brain of animals was established [21, 22]. In 1988, Santos *et al.* reported the formation of Ang-(1-7) from Ang I by an ACE-independent pathway [23].

In 2000, almost half a century after the discovery of ACE by Donoghue *et al.*, Tipnis *et al.* cloned the main mediator of the non-classical RAS axis – an enzyme-related carboxypeptidase (ACE2), a homologue of ACE but with novel characteristics [24]. The new enzyme converted Ang I into Ang-(1-9) [4]. In addition, important alternatives to ACE and ACE2 to convert Ang I and Ang II into Ang-(1-7) in cells and organs by prolyl carboxypeptidase and neutral endopeptidase (neprilysin, NEP) were discovered [25, 26].

The understanding of the functional role of Ang-(1-7)

Table 1. Historical research of the renin-angiotensin system.

Substrate	Year	Researchers	Scientific Value
Renin	1898	Tigerstedt R *et al.* [8]	Presure effect.
	1934	Goldblatt H *et al.* [9]	
Angiotonin (angiotensin)	1939	Braun-Menéndez E *et al.* [10]	Vasoconstriction.
	1940	Page IH *et al.* [11]	
Ang I, Ang II	1954	Skeggs L *et al.* [12]	Identification of two forms of angiotensin.
ACE	1956	Skeggs L *et al.* [13]	ACE catalyses the conversion of Ang I into Ang II.
Ang-(1-7)	1968	Yang HY *et al.* [5]	Description of heptapeptide Des-phe- Ang II.
	1988	Santos RA *et al.* [23]	Conversion of Ang II into Ang-(1-7).
Ang III	1976	Chiu AT *et al.* [16]	Ang III is generated from Ang I by ACE.
Mas receptor	1986	Young D *et al.* [6]	Ang-(1-7) is an endogenous ligand for the G protein-coupled Mas receptor.
AT_1 & AT_2 receptors	1989	Chiu AT *et al.* [18]	Two types of Ang II receptors were identified.
	1991	Sasaki K *et al.* [19]	
		Murphy TJ *et al.* [20]	
ACE2	2000	Tipnis SR et al [24]	ACE2 is responsible for conversion of Ang II into Ang-(1-7).
		Donoghue M *et al.* [4]	
	2002	Crackower MA *et al.* [61]	ACE2 is the regulator of cardiac function and has the cardioprotective effects.
Neprilysin	1998	Ferrario CM *et al.* [25]	Alternatives to ACE and ACE2 to convert Ang II and Ang-(1-9) into Ang-(1-7).
Prolyl carboxypeptidase	2013	Grobe N *et al.* [26]	
ACE2 and coronaviruses	2003	Li W *et al.* [28]	ACE2 protease domain as the receptor for SARS-CoV and for SARS-CoV-2.
	2020	Walls AC *et al.* [29]	

Notes: AT_1 receptors – angiotensin type 1 receptors; AT_2 receptors – angiotensin type 2 receptors; ACE – angiotensin-converting enzyme; ACE2 - angiotensin-converting enzyme 2.

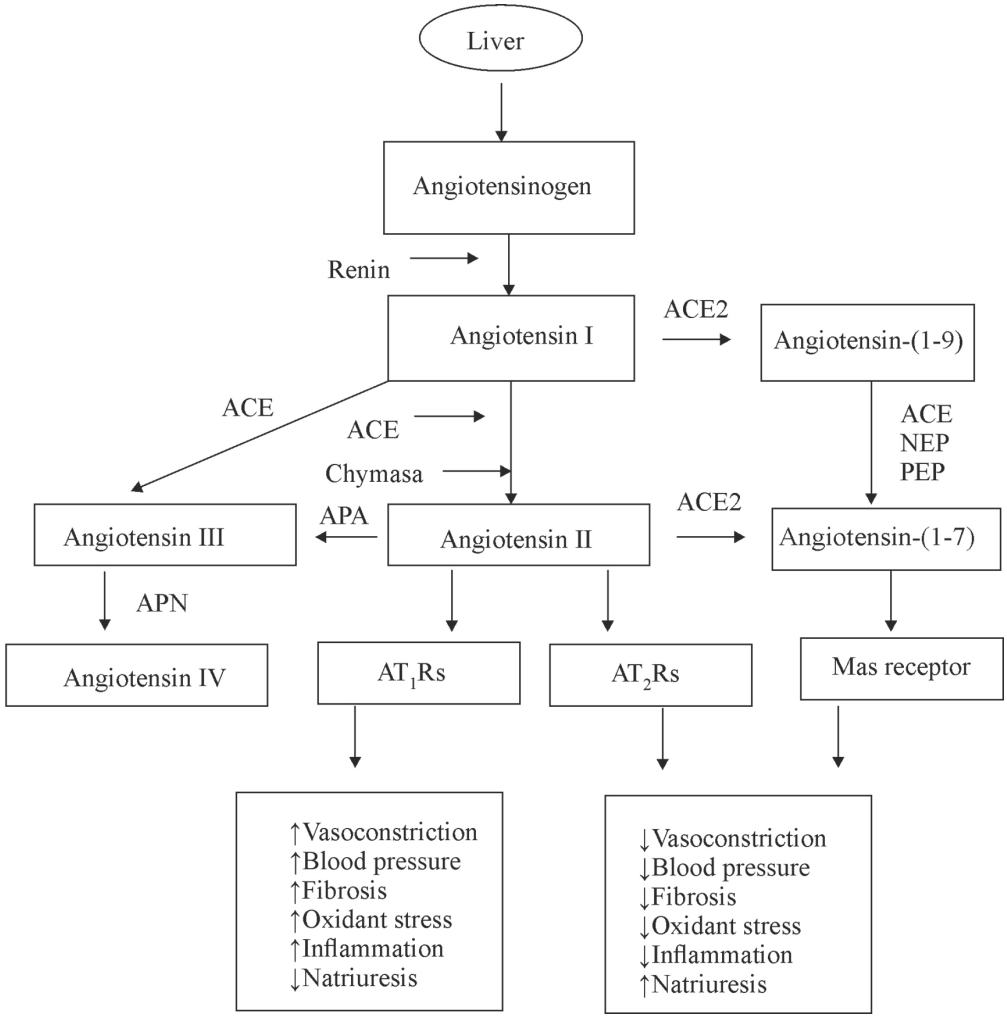

Figure 1. The renin-angiotensin system cascade (APA – aminopeptidase A; PEP – prolyl endopeptidase; NEP – neutral endopeptidase neprilysin).

has expanded due to studies of the Mas, a G protein-coupled receptor that was first described in 1986 as a Mas oncogene (the name is the first 3 surname letters of the patient (Massey) whose tumor cells were used to identify the gene) [6].

Thus, based on previous studies, the following sequence was developed to represent the concept of the classical RAS: angiotensinogen - Ang I - ACE - Ang II - AT_1 receptor and AT_2 receptor. In line with scientific advances, the concept of the non-classical RAS axis was developed: ACE2-Ang-(1-7) -Mas receptor. The RAS cascade is presented in Fig. 1.

Due to the epidemiological situation caused by coronavirus infection, the research has revealed unexpected data regarding the RAS. In addition to the homeostatic regulation of the cardiovascular system, the RAS has been found to have other functions [27]. In 2003, the protease domain of ACE2 was found to be a functional receptor for severe acute respiratory syndrome coronavirus (SARS-CoV) causing SARS [28]. Against the background of the global pandemic of coronavirus disease 2019, COVID-19 (CO – corona, VI – virus, D – disease), ACE2 was found to serve as the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well, since SARS-CoV-2, similar to SARS-CoV, utilizes ACE2 to gain entry into human cells [29]. Two forms of ACE2, membrane-bound (mACE2) and soluble (sACE2), were discovered. The full-length mACE2 is present on the cell membrane and consists of a transmembrane anchor and an extracellular domain, while the sACE2 lacks the membrane anchor and circulates in small amounts in the blood [30]. Due to the epidemiological situation, understanding the RAS – SARS-CoV-2 axis, especially the interaction between COVID-19 and ACE2, relevant to pathogenesis, clinical course, and outcomes of coronavirus infection should be under scrutiny.

Thus, multifunctional components of the RAS have been studied over three centuries. The number of publications in the PubMed database from 1962 to 2022 with the keywords “renin-angiotensin system” has increased, indicating the growing scientific interest in this issue (Fig. 2).

The explanation of this trend is as follows: firstly, the classical RAS is involved in the pathogenesis and clinical outcomes of multiple cardiovascular pathology, renal diseases, endocrine disorders. Based on these data, a pharmacological class of medications widely used to treat hypertension, heart failure, chronic kidney disease, diabetes

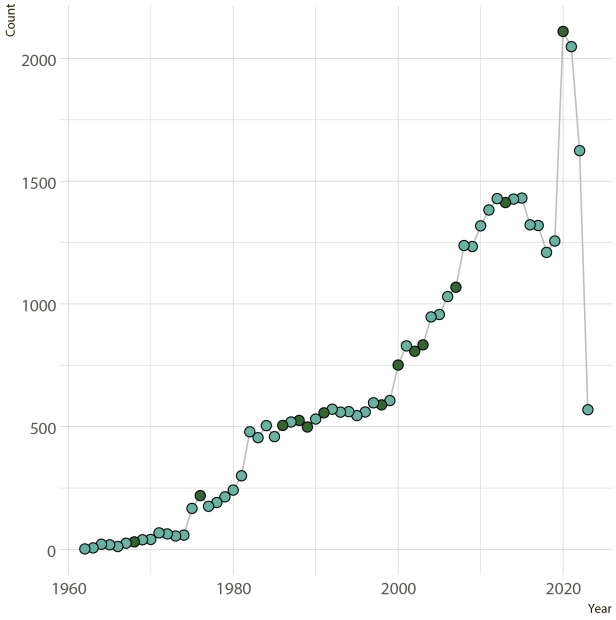

Figure 2. Bibliometric analysis of the PubMed database.

mellitus (DM) has been developed and this is an ongoing process. Secondly, new insights into biological effects of the non-classical RAS have appeared, stimulating further research aimed at the development of new drugs. Finally, in the pandemic era, significant attention to the RAS alongside with advanced knowledge of the protease domain of ACE2 acting as a functional receptor for coronavirus SARS-CoV and SARS-CoV-2 have generated a publication surge. Novel approaches are needed for comprehensive understanding the relationship between the RAS and COVID-19.

Biological Effects of RAS Components

The RAS is responsible for basic physiological processes and is involved in the development of diseases affecting various organs of the body. The RAS comprises the classical axis which begins with the cleavage of angiotensinogen synthesized mainly by the liver under the action of renin, which was extracted from the kidney as a hypertensive factor by physiologists Robert Tigerstedt and Per Bergman [8].

Renin is synthesized in the kidney by the juxtaglomerular body as preprorenin in response to triggering factors such as decreased intrarenal pressure, depleted volume of circulating blood and fluid, changes in electrolyte balance, hypoxia [31–33]. Renin catalyzes the conversion of angiotensinogen into Ang I which has little pressor activity. ACE is the main enzyme of the RAS; it catalyzes the conversion of Ang I into Ang II [34].

Based on data collected by various researchers in previous years, the main effector peptide of the classical RAS pathway is the octapeptide Ang II. It is considered a systemic circulating hormone but is locally present in organs and tissues responsible for the regulation of cardiorenal homeostasis [35]. The interaction between Ang II and the sympathoadrenal system is of great importance as it stimulates the secretion of biologically active substances, adrenaline from the adrenal medulla and aldosterone from the adrenal cortex in particular [36, 37]. Therefore, a more comprehensive study of this cascade of RAS transformations – renin-angiotensin-aldosterone, is reasonable.

Ang II is considered a leading regulator of blood pressure as it induces contraction of vascular smooth muscle and has direct growth-promoting effects on cardiac myocytes, fibroblasts, and vascular smooth muscle cells causing cardiovascular remodeling [38, 39].

The biological effects of Ang II are mediated by specific cell membrane receptors (AT_1 and AT_2 receptors) that are widely distributed in both humans and animals and are found in the heart, cardiac fibroblasts, kidneys, and other organs [40, 41].

The main effects of Ang II are realized via AT_1 receptors, namely sodium retention, vasoconstriction, stimulation of aldosterone secretion, initiation of the pro-inflammatory cascade, oxidative stress, and arterial hypertension [42–45]. Stimulation of AT_1 receptors leads to proliferative processes in the heart and blood vessels resulting in myocardial hypertrophy and vascular remodeling [46, 47]. Activation of the sympathoadrenal system through AT_1 receptors is characterized by an increase in myocardial excitability with subsequent development of arrhythmias [48].

AT_2 receptors are widely distributed in the body and are present in the heart, central nervous system, vascular endothelium, kidneys, and others organs [49–51]. AT_2 receptors act as the physiological counterbalance of AT_1 receptors. Activation of AT_2 receptors can directly counteract the AT_1 receptor-dependent effects of Ang II through heterodimerization of both receptors on the cell surface and cause vasodilation and proliferation inhibition, antagonize the growth and oxidant effects of AT_1 receptors [52–54], in addition to reducing blood pressure [55]. Lo *et al.* reported that the activation of AT_2 receptors blunted pressure-natriuresis in rats [56].

Significant progress in defining biochemical components, physiological effects, and fundamental role of the RAS was made in 2000 with the discovery of ACE2, a homologue of ACE. ACE2 is a Type 1 integral transmembrane glycoprotein which catalyzes the conversion of Ang I into Ang-(1-9) and Ang II into Ang-(1-7) by removing the COOH-terminal amino acid phenylalanine [4]. It is present in many cell types and tissues including the heart (cardiomyocytes, endothelial cells, epicardial adipose tissue) and kidneys which indicates its possible role in cardiorenal function [57, 58]. Using a Northern blotting approach for quantitative mRNA expression profiling of ACE2, Harmer *et al.* confirmed that ACE2 was expressed at high levels in gastrointestinal, renal, and cardiovascular tissues; ACE2 expression in the ileum and duodenum was significantly higher as compared to that in renal and cardiovascular tissues [59]. Based on an immunohistochemical study of healthy people, ACE2 was high in the upper respiratory epithelium, nasal and oral mucosa, reaching the maximum level in type 2 pneumocytes [60].

Crackower *et al.* firstly determined that ACE2 was the regulator of heart function with cardioprotective effects [61]. ACE2 is the dominant link in the biochemical cascade involved in reducing the damaging effect of

the RAS by targeting Ang II, thereby suppressing its actions to increase the activity of the sympathoadrenal system, increase blood pressure, stimulate fibrosis and myocardial hypertrophy [62]. According to modern concepts, the alternative axis is a key modulator of the RAS, since ACE2 and Ang-(1-7), via their interaction with the Mas receptor, play a significant role in the physiological and pathophysiological processes due to their biological effects [63]. Ang-(1-7) opposed the pressor effect of Ang II and reduced blood pressure in spontaneously hypertensive rats [63]. Release of nitric oxide by Ang-(1-7) from porcine coronary endothelium caused canine coronary vasodilation via kinins and nitric oxide and mediated the activation of endothelial nitric oxide synthase via the Mas receptor [64]. In a study by Handa *et al.*, Ang-(1-7) altered fluid absorption in the renal tubules and increased natriuresis [65]. Ang-(1-7) was found to act as an endogenous regulator of cell growth. The anti-hypertrophic effects of Ang-(1-7) were mediated by the coupling of the peptide to the Mas receptor [66]. Thus, ACE2 exhibits a protective effect on multiple cardiovascular and renal functions through its interaction with the Mas receptor and has an effect opposite to the classical RAS.

Neutral endopeptidase neprilysin (NEP) is a part of the RAS counter-regulatory system. Neprilysin is an integral membrane zinc-containing endopeptidase, which degrades and inactivates a number of bioactive peptides [67]. NEP cleaves several peptides such as Ang I-II into inactive fragments, is an alternative to ACE to convert Ang II into Ang-(1-7) and reduces the serum levels of all these peptides [68]. NEP inhibition increases plasma Ang II concentration and augments the vasoconstrictor response to exogenous angiotensin [69].

The components of the non-classical RAS - ACE2/Ang-(1-7) /Mas-receptor axis, and a component of the classical axis – AT_2 receptors, are of great importance for counteracting the negative effects of the classical A II/AT_1 receptor axis.

Renin-Angiotensin System and Coronaviral Infections

The twenty-first century has witnessed life-threatening acute respiratory infection caused by coronaviruses. The SARS-CoV-1 virus caused the 2002-2004 SARS outbreak in China. In December 2019, a novel coronavirus, SARS-CoV-2 emerged in Wuhan, China and caused an outbreak of acute respiratory disease COVID-19 [70].

While studying the features of these viruses, the involvement of the RAS in viral infection, pathogenicity, and clinical course of coronavirus diseases has been revealed. The ambiguity of these data and the current controversy that constantly arises when considering previous finding are relevant to the interactions of coronaviruses SARS-CoV and SARS-CoV-2 with ACE2 [28, 29]. Recent mechanistic and structural analyses indicated that for entry of SARS-CoV-2 into host cells, the viral spike (S) protein of SARS-CoV-2 is activated through proteolytic cleavage, attaches to ACE2 receptor and enters the transmembrane serine protease 2 (TMPRSS2) of host cells leading to fusion of a viral membrane with the host cell membrane during viral entry; thus, ACE2 receptor should be considered as a gateway of SARS-CoV-2 [71].

Studying the role of the RAS, especially ACE2 and its receptors, in these coronavirus infections has prompted researchers to comprehensively investigate the RAS with an emphasis on the pathogenetic significance and therapeutic potential of its non-classical components to optimize diagnosis, prognosis, and treatment outcomes in patients with SARS coronavirus-induced lung injury [72]. SARS-CoV-2 was found to use ACE2 for invading the host cells even more than SARS-CoV, as SARS-CoV-2 binded ACE2 with 10- to 20-fold higher affinity than SAR-CoV [73]. These data explain the mechanism contributing to the severity of SARS-CoV-2 infectivity and pathogenicity.

The interaction of SARS-CoV and SARS-CoV-2 with the RAS results in downregulation of ACE2 and all other components of the RAS, activation of the classical RAS. Ang II accumulation due to the unopposed RAS activation via Ang II/AT_1 receptors and the loss of ACE2-mediated health protection cause organ injuries and systemic adverse effects [74].

ACE2, the key functional receptor of SARS-CoV-2, plays a crucial role in the pathogenesis of COVID-19 due to complex molecular mechanisms that contribute to the transmission of the virus and subsequent development of clinical manifestations. Osman *et al.* reported that during COVID-19, expression of ACE2 mRNA and cell-surface ACE2 reduced, Ang II was no longer metabolized by ACE2, and its plasma concentrations increased [75]. In an in-vitro study of human airway epithelial cells by Imai *et al.*, low ACE2 expression was associated with increased phenotype severity. The authors reported the loss of ACE2 in knockout mice led to impaired oxygenation and increased inflammation [76].

According to the report on 72,314 cases from the Chinese Center for Disease Control and Prevention, in over 44,000 patients with confirmed COVID-19, the most common comorbidities included hypertension, chronic respiratory disease, DM, cardiovascular disease [77]. Comorbidities increase the susceptibility to infections and raise the likelihood of developing severe and fatal complications. The risk of severe COVID-19 disease or death is higher in patients with cardiovascular pathologies, DM, and obesity [78–80]. The dysregulation of the RAS could be an important link between cardiovascular pathology, DM, obesity, and COVID-19 severity. The RAS is involved in the pathogenesis of overspreading diseases [1–3, 81], while SARS-CoV and SARS-CoV-2 infections change the surface expression of the binding protein ACE2, a pivotal component for host cell entry [74–76].

Despite numerous studies related to the classicsl and non-classical RAS in context of COVID-19, there is still no clear understanding of the integration of SARS-CoV-2 with ACE2 expression and/or its regulation. It is important to identify RAS-targeted therapeutic strategies that can improve clinical outcomes in patients with COVID-19.

Conclusions

Thus, the discovery of RAS at the end of the 19th century has sparked a multitude of research projects that have contributed to the in-depth definition of this system as the leading regulator of human body functions. Further thorough research is needed to involve the key interrelated aspects of the pathogenesis of many diseases and to implement new knowledge into medical practice. A broad range of physiological and pathophysiological RAS effects are a prerequisite for developing new drugs with clinical translation potential. For future perspectives, a comprehensive study of modulating factors addressed to shifting the balance of the classical and alternative RAS axis to unfavourable side in patient with COVID-19 by improving therapeutic approach requires special attention.

Ethical Statement & Informed Consent

This article does not involve any new data collection from human or animal subjects. Therefore, no ethical statement or informed consent is required.

Data Availability

Data sharing policy is not applicable due to no new data were generated.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

The authors declare that the review was conducted in the absence of any commercial or financial support.

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