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Review

Induced dysregulation of ACE2 by SARS-CoV-2 plays a key role in COVID-19 severity

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of COVID-19, is reported to increase the rate of mortality worldwide. COVID-19 is associated with acute respiratory symptoms as well as blood coagulation in the vessels (thrombosis), heart attack and stroke. Given the requirement of angiotensin converting enzyme 2 (ACE2) receptor for SARS-CoV-2 entry into host cells, here we discuss how the downregulation of ACE2 in the COVID-19 patients and virus-induced shift in ACE2 catalytic equilibrium, change the concentrations of substrates such as angiotensin II, apelin-13, dynorphin-13, and products such as angiotensin (1–7), angiotensin (1–9), apelin-12, dynorphin-12 in the human body. Substrates accumulation ultimately induces inflammation, angiogenesis, thrombosis, neuronal and tissue damage while diminished products lead to the loss of the anti-inflammatory, anti-thrombotic and anti-angiogenic responses. In this review, we focus on the viral-induced imbalance between ACE2 substrates and products which exacerbates the severity of COVID-19. Considering the roadmap, we propose multiple therapeutic strategies aiming to rebalance the products of ACE2 and to ameliorate the symptoms of the disease.

1. Introduction

SARS-CoV-2 enters the host cells mainly by targeting the Angiotensin Converting Enzyme 2 (ACE2) receptors that is highly expressed in lungs. As ACE2 is expressed in endothelial cells and also throughout the body, COVID-19 can be associated with other symptoms such as hypertension, thrombosis, pulmonary embolism and endothelial dysfunction [1].

ACE2, a key enzyme in renin-angiotensin system, binds to a range of substrates including Angiotensin I (Ang I), Angiotensin II (Ang II), apelin-13, neurotensin- (1–11), dynorphin A-(1–13), β-casomorphin-(1–7), and ghrelin [2]. SARS-CoV-2 interacts with ACE2 receptors via the surface glycoprotein S (homotrimer) [3,4]. ACE2 has been identified as the main receptor for the binding of the SARS-CoV-2 protein S to the host cells. Other studies have shown that transmembrane serine protease

2 (TMPRSS2) [5], sialic acid receptors and extracellular matrix metalloproteinase may also mediate the entry of the virus to some extent [6]. The N-terminal of the SARS-CoV-2 glycoprotein contains a peptide signal, S1 and S2 subunits. S1 subunit binds to the peptidase domain of ACE2 via receptor binding domain (RBD) and S2 subunit mediates the fusion of viral membrane and host cell membrane, and facilitates the viral genomes entry into the host cells [3,7].

Host protease-induced cleavage and dissociation of protein S are essential for infection [4]. Protein S is cleaved to a receptor-bound N-terminal S1 subunit and a C-terminal membrane fusion S2 subunit by host proteases such as type II transmembrane serine proteases (TTSPs), HAT, catepsin B and L (pH-dependent endolysosomal protease), elastase, trypsin and furin. A lysosomal protease then cleaves the S2 at S2′ and releases the hydrophobic fusion peptide for integration into

the host cell membrane [8,9].

Sequence homology studies identified several aminoacid replacement in RBD of SARS-CoV-2 protein S in comparison with SARS-CoV which increases the affinity to ACE2 and strengthen the interactions between them. The interaction site is bigger in SARS-CoV-2 than SARS-CoV, as 21 and 17 aminoacides contribute to direct interaction with ACE2, respectively [10–12]. Shang et al. reported that, unlike SARS-CoV, the cells infected by SARS-CoV-2 induce the proprotein convertase furin-mediated protein S pre-activation which increase the affinity of RBD to ACE2. This leads to efficient the virus entry into the host cells and also facilitates the escape of the virus from immune machinery. The authors hypothesized that this is the reason for high rate of the virus spread [11,13]. Most of our knowledge about SARS-CoV-2 entery into the cells originates from SARS-CoV. Therefore, it has been suggested that once SARS-CoV-2 binds to ACE-2 receptor, fusion peptide (FP) in S2 subunit interacts with lipid layers in host cell membrane and induces the fusion of the virus and host membranes and formtion of endosomes, in which cysteine proteases cathepsin B and L and serine protease TMPRSS2 cleave protein S and faciliate the release of viral genome into the cytoplasm [13]. However, much remained to be discovered on how spike protein is cleaved by the proteases.

Xia et al. showed that unlike SARS-CoV, an additional RRAR motif exists in SARS-CoV-2 S1/S2 cleavage site. This motif is a furin cleavage site (FCS) that might be cleaved by furin-like enzymes and facilitate virus spread and infection [14,15]. Huang et al. and Hoffmann showed that serine protease TMPRSS2 on host cell membrane might activate SARS-CoV-2 spike protein to enhance endosome-mediated viral entry into the cells [4,11].

Based on a previous report virus-bound ACE-2 endocytosis is pH dependent and requires acidic pH (pH 3). Therefore, lysosome and endosome acidic pH activates cathepsin B and L which in turn induce the cleavage of glycoprotein S to S1 and S2 subunits. S1 binds to ACE-2 and S2 is used for membrane fusion [16].

The contribution of a range of proteases to virus-ACE2 interaction can explain many aspects of SARS-CoV-2 pathogenesis. Hoffmann et al. demonstrated that the inhibition of TMPRSS2 serine protease by camostat mesylate blocked SARS-CoV-2 infection of lung cells. They concluded that TMPRSS2 plays a role in priming the viral spike protein to enter the cells. According to the later research, the full inhibition of viral infection is attained when endosomal cathepsin L and B (cysteine proteases) and TMPRSS2 are co-inhibited by E-64d and camostat mesylate respectively. In addition, ammonium choloride strongly inhibited viral entry into the TMPRSS2⁻293T cells implied the ammonium choloride-induced inhibition of endosomal cathepsin L and B cysteine proteases [4].

In cells, virus amplification takes place by viral RNA polymerase and the viruses then infect the surrounding cells.This might lead to organ dysfunction and faster spread of the virus. Coronaviruses forms bilayer vesicles and prevents the expression of Receptor Recognition Pattern (PRP) and thus, immune system fails to recognize the viral particles [16–18].

The entry of the SARS-CoV-2 and SARS-CoV depends ACE-2 [19–21], SARS-CoV-2 downregulates ACE2 expression similar to SARS-CoV [21, 22]. However, sialic acid of the glycoproteins on the surface of host cell may also act as the receptor for hemagglutinin esterase (HE) on SARS-CoV-2. HE contains a carbohydrate binding domain (lectin) linked to a domain with esterase activity. HE binds to sialic acid moieties and facilitates the virus entry. It seems that HE-mediated fusion of the virus and host cell membrane are necessary for the entry of SARS-CoV-2 [23, 24]. ACE2 is the well-known receptor for the entry of SARS-CoV-2 [1]. ACE2 dysregulation changes the equilibrium of the ACE2-catalyzed reaction. As a result, ACE2 substrates are accumulated while the concentrations of its products are decreased. This might worsen the pathology of the disease and may lead to death. Thereby, ACE2 functions will be reviewed and discussed in detail to elucidate the effects of ACE2 dysregulation upon the entry of the SARS-COV-2.

2. ACE2

ACE2 is a cell-surface non-raft protein with the extracellular N-terminal and intracellular C-terminal domains. Binding to SARS-CoV-2 protein S induces the ACE2 internalization [25]. ACE2 is mainly expressed in cardiac muscle cells, cardiac fibroblasts, the coronary vascular endothelium, kidney, liver, small intestine, testes, brain, lung alveolar epithelial cells, lymphocytes within oral mucosa, enterocytes, arterial and venous endothelial cells as well as arterial smooth muscle cells [26–32].

ACE2 is a transmembrane protein, however, a low level of soluble form is detectable in the plasma of patients with COVID-19 [33]. Compared with apical and basolateral localization of ACE, ACE2 is mainly on the apical cell surface [34]. Although ACE2 is a similar carboxypeptidase to ACE (EC 3.4.15.1) with 42% sequence similarity, it is a mono-carboxypeptidase (cleaves one amino acid from the substrate) and ACE is a dipeptidyl-carboxypeptidase which cleaves a dipeptide at the C-terminal of substrate [35,36].

Enzyme structure contains a signal peptide, transmembrane domain and Zn^{2+}-binding active site. Catalytic site is exposed to vasoactive peptides [35]. ACE inhibitory antibodies do not inhibit the ACE-2, in spite of the similar structures [35,36].

In contrast, ACE2 is overexpressed in patients treated with ACE inhibitory antibodies [37,38]. ACE2 converts Ang II to Angiotensin (1–7) (Ang 1–7), Ang I to angiotensin 1–9 (Ang 1–9), apelin (1–13) to apelin (1–12), dynorphin A (1–13) to dynorphin (1–12), β-casomorphin (1–7) to β-casomorphin (1-6) [2]. ACE2 is a potential regulator of renin angiotensin system (RAS). SARS-CoV-2 interaction with ACE2, interferes RAS and enhances the severity of acute respiratory symptoms [39]. Since SARS-CoV-2 infection is associated with a downregulation of ACE2 expression [21], this can exacerbates the COVID-19 symptoms. For better understanding of the harmful effects of the accumulation of ACE2 substrates and decrease in the concentrations of the products due to the ACE2 viral- induced dysregulation, we have a closer look at the substrates and products (Table 1). In this review, we focus on the consequences of the SARS-CoV-2 induced imbalance between ACE2 substrates and products aiming to discover the relation among substrates accumulation, decreased products and disease complications to propose therapeutic strategies.

3. Ang II

In RAS, Angiotensin I is produced from angiotensinogen by the action of renin (released from kidney juxtaglomerular cells) [40]. Ang I is converted to Ang II by the catalytic activity of ACE particularly in pulmonary endothelial, plasma, kidney, brain and heart coronaries. In rat model, Ang II, with a half-life of approximately 16 s in plasma [41], is quickly converted to either Ang (1–7) by ACE2 or Ang III by angiotensinases [42]. Ang II is an active octapeptide which triggers its physiological functions by binding to Angiotensin II receptor type 1 (AT-1) (Fig. 1), AT-2 and AT-4 receptors [43]. The main functions of AT-1 mediated Ang II [44] are vasocontraction [45], inotropy and cardiac regeneration (via myocard receptors), sympathetic nervous system enhancement [46], vasopressin diffusion, regulation of peripheral sympathetic nervous system and pituitary, regulation of aldosterone secretion (via receptors in adrenal glands) [47]. AT-2 receptors are widely expressed in emberyonic tissues, however their expression is limited to adrenal gland, vascular endothelial, brain, kidney and ovary, which acts as vasodilator by releasing bradykinin and nitric oxide [48]. AT-2 mediates anti-inflammatory in vitro and in vivo [49,50] and anti-proliferating responses in rat pheochromocytoma cell line.

[51,52] which attenuates AT-1 signaling in turn. Moreover, it seems that AT-4 regulates extracellular matrix in central nervous system and modulates oxytocin diffusion [53,54].

Ang II stimulates inflammatory responses, via AT-1, in leukocytes, endothelial cells and smooth muscle cells by activating NF-κB which

Table 1
Properties of the main substrates and products of ACE2.

Factors	Sequence	kcat/Km	Half-life	Circulation levels	Receptor	Ref
Ang I[1]	DRVYIHPFH↓L	4.9×10^3	–	–	–	[2]
Ang 1–9[2]	DRVYIHPFH	–	–		AT2R[5]	
Ang II[3]	DRVYIHP↓F	1.8×10^6	15 min in heart, kidney, and adrenal, 0.5 min in circulation (in pigs)	5–50 fmol/ml (in human, mouse, and rat plasma)	AT1R[6]	[227, 228]
Ang 1–7[4]	DRVYIHP	–	9 s in rat, 0.5 h in human	5–80 fmol/ml (in human, mouse, and rat plasma), in human 20 pg/ml	Mas R[7]	[227, 229]
Apein 1–13	QRPRLSHKGPMP↓F	2×10^6	Less than 3 min in rat and less than 8 min in human		APJ[8]	[2,163]
Apelin 1–12	QRPRLSHKGPMP	–	10–15 min in human plasma		APJ	[161]
Dynorphin A 1–13	YGGFLRRIRPKL↓K	2.9×10^6	Less than 1 min in human blood (ex vivo)		KOP[9], NADM[10]	[2,230]
Dynorphin A 1–12	YGGFLRRIRPKL	–	–	–	KOP	[2,231]

1: Angiotensin I, 2: Angiotensin 1–9, 3: Angiotensin 1–7, 5: angiotensin II type-2 receptor, 6: angiotensin II type-1 receptor, 7: Mas receptor, 8: apelin receptor, 9: κ-opioid receptor, 10: N-Methyl-D-aspartate receptor.

altogether enhance the transcription of TNF-α, IL-1 and Interleukin 6 (IL-6) [55], adhesive molecules such as E-selectin and P-selectin, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), different chemokines and other proinflammatory factors [56]. These functions of Ang II are consistent with the findings from COVID-19 patients where SARS-CoV-2 entry to pulmonary cells was associated with high secretion of inflammatory cytokines like IL-1β, IL-6 and TNFα [1,57]. Among all, IL-6 is known to be one of the strongest predictors of death during hospitalization [58]. Downregulation of ACE-2 in COVID-19 patients can lead to Ang II accumulation [57,59]. Studies on patient samples and animal models have shown that Ang II binding to AT-1 can further internalize ACE2 through extracellular signal-regulated kinases (ERK1/2) and P38 mitogen-activated protein kinase (MAPK) signaling and hence downregulates ACE2 [60,61]. Hypertension in COVID-19 patients [62–64] might be severed by Ang II accumulation which activates proinflammatory signaling [65]. Clinical studies have shown that arterial pressure is correlated to increased plasma inflammatory mediators and vascular inflammation. In hypertensive patients circulating monocytes, lymphocytes and pro-inflammatory cytokines such as TNF-α, IL-6 and C-reactive protein (CRP) are increased [66–68].

Accumulated Ang II can be metabolized to Ang IV by aminopeptidase A [69]. Ang IV binds to AT-4 receptor [54]. Accumulation of Ang II (in mice model) and Ang IV (in rat model) can increase the likeliness of thrombosis by increasing the plasminogen activator inhibitor-1 (PAI-1) [70–72]. Thrombotic role of Ang II can be explained by overexpressing and activating endothelin-1 as PAI-1 activator [65,73]. Ang II-stimulated inflammation influences the vascular permeability in rat endothelial cells [74], alters vascular morphogenic responses, leukocyte attachment to endothelium (in rat model) [75] and platelet accumulation in human platelet rich plasma (*in vitro* study) [76,77]. Hypertension is prevalent among the COVID-19 patients and might be induced by Ang II accumulation associated with accumulation of platelets, platelet dysfunction, deficient fibrinolysis and coagulation [71,78]. Therefore, thrombosis in COVID-19 patients can be attributed to harmful effects of Ang II accumulation due to dysregulation of ACE2 after the entry of the SARS-CoV-2 into host cells [8,79]. COVID-19 patients have more or less impaired coagulation system which increases the rate of ischemic mortality [80,81]. Acute pulmonary embolism in COVID-19 patients is one of the important predictor of clinical deterioration during viral pneumonia [82–84]. Therefore, a constant checking of the coagulation markers such a Prothrombin Time/Partial Thromboplastin Time (PT/PTT), fibrinogen, D-dimer and prescribing the anticoagulation agents like heparin has been recommended for patients with D-dimer value above normal range (4 times higher in COVID-19 patients) [1].

Ang II also acts as a pathologic mechanism in angiogenesis during hypoxia. Ang II upregulates angiopoietin-2, the factor that binds to TEK receptor tyrosine kinase (Tie2) and induces angiogenesis. At the early stages of angiogenesis, angiopoietin-2 antagonizes Tie2 and inhibits angiopoietin-1/Tie2 signaling axis. Cornea micropocket assay has showed that the angiopoietin induces neovascularization in mice mediated by vascular endothelial growth factor (VEGF) [85,86]. This allows VEGF and other growth factors to enhance the migration of endothelial cells, and form new vessels [85,86]. Consequently, angiopoietin-1 is increased while angiopoietin-2 is decreased [87,88]. However, angiopoietin-1 activates Tie2 and induces endothelial survival as well as vessel maturation [87,88]. Therefore, the ratio of angiopoietin-2 to angiopoietin-1 is well controlled during angiogenesis and shifts toward either of the proteins associated with pathological conditions [87,88]. Angiopoietin-2 is increased during acute respiratory distress syndrome (ARDS) in COVID-19 patients [89]. This is consistent with the increased (angiopoietin-2)/(angiopoietin-1) ratio in ALI/ARDS patients. Increased Angiopoetin-2 can be a prognosis marker for lethality [90]. Ang II upregulates angiopoietin-2 and increases angioprotein-2 as well as VEGF expression and thus play a key role in increasing vascular permeability in patients with acute pulmonary injury [91]. Vascular permeability is increased in patients with acute respiratory syndrome as a result of hypoxia-induced VEGF expression [92]. and focal adhesion tyrosine kinase (FAK) induced inflammatory responses [93]. Angioprotein-2 has been shown to induce inflammation and cell death during hypoxia *in vivo* as well as epithelial necrosis in mouse lung epithelial cell and mice *in vitro* (hyperoxia causes angiopoietin 2–mediated acute lung injury and necrotic cell death).

These raise the possibility that Ang II-induced angiogenesis and high vascular permeability worsen the pathology of the COVID-19 [8]. Regarding the role of Ang II in the induction of oxidative stress, Ang II phosphorylates c-Src, [the regulator of NOX (a family of NAD(P)H oxidases) that is the main source of reactive oxygen species (ROS)] [94,95]. In addition, Ang II facilitates ROS generation by the mitochondrial potential depolarization [96]. There is evidence that Ang II downregulates the ROS scavengers and hence increases ROS [97]. ROS activates redox-sensitive transcription factors like activator protein 1 (AP-1) and NF-κB [98], leading to vascular permeability, leukocyte infiltration, and etc [98]. As oxidative stress is generated during coronavirus induced ADRS, COVID-19 patients show the aforementioned symptoms due to Ang II accumulation and impaired ACE2 signaling axis, less access of endothelial cells to nitric oxide (NO) and oxidative stress [99]. Moreover, the increased ROS during oxidative stress can upregulate VEGF in macrophages and endothelial cells [100,101]. ROS induces Hypoxia-Inducible Factor 1-alpha (HIF1-α) and Ets-1 and resulting in VEGF upregulation [102]. By-products of ROS such as lipid peroxide can interact with VEGFR2 and induce angiogenesis *in vivo* [103]. Multiple *in vitro* studies on normal and tumor cell types have shown that the lipid oxidation products increase VEGF which induces angiogenesis in association with IL-8 and COX-2 products [104]. Animal studies have shown that lipid oxidation products can induce angiogenesis through
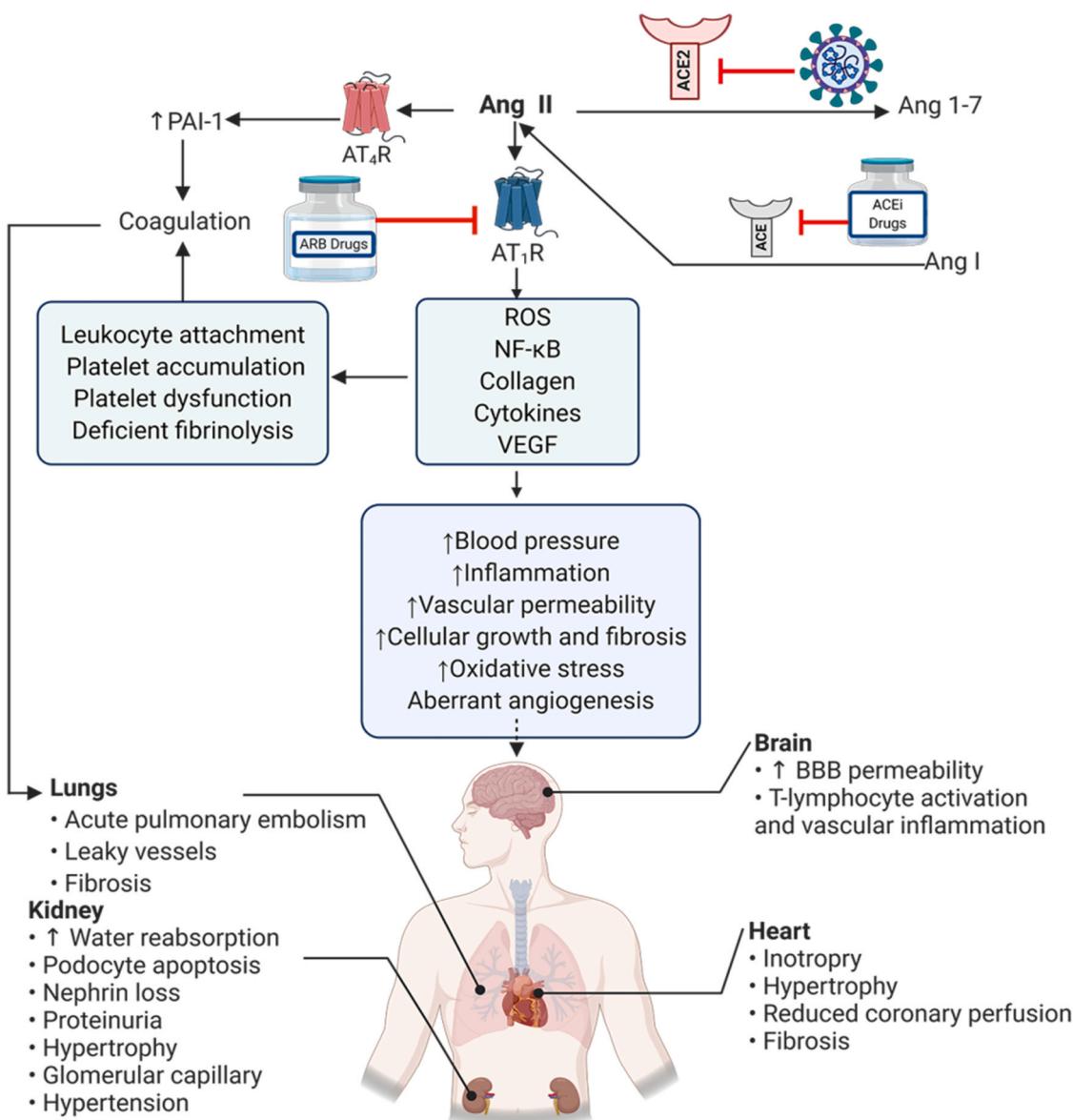
Fig. 1. Effects of Ang II on organs. ACE degrades Ang I and produces Ang II which binds to its receptors (ATRs). Then, ACE2 converts Ang II into Ang 1–7. SARS-CoV-2 downregulates the expression of ACE2 and causes the pathological symptoms in several human organs due to accumulation of Ang II (Created in BioRender.com). Ang I: angiotensin I, Ang II angiotensin II, Ang 1–7. angiotensin 1–7, ACE: angiotensin-converting enzyme, ACE2: angiotensin-converting enzyme2, AT1R: Angiotensin II receptor type 1, AT4R: Angiotensin II receptor type 4, PAI-1: Plasminogen activator inhibitor-1 ROS: Reactive Oxygen Species, VEGF: Vascular endothelial growth factor, ARB drugs: angiotensin II receptor blocker drugs, ACEi drugs: Angiotensin-converting enzyme inhibitor drugs, BBB: blood–brain barrier.

VEGF-independent Toll-like receptor (TLR) 2/MyD88 dependent signaling (Fig. 1) [105].

As discussed above, Ang II can affect the severity of COVID-19. A recent study in human (non-hypertensive patients) showed that there is a correlation between the plasma concentration of Ang II and severity of COVID-19 [59]. Since it negatively regulates the activity of ACE2 and also plays a role in hypertension, infalamation, oxidative stress and angiogenesis whose accumulation may lead to severity of COVID-19.

4. Ang (1–7)

Ang II is mainly degraded by ACE2 and to some extent by pro-lylcarboxypeptidase (PRCP) and prolyloligopeptidase (POP/PEP/PREP/PE), where these carboxypeptidases remove the C-terminal phenylalanine from Ang II [33]. In contrast to Ang II, Ang (1–7) is a biologically active peptide and acts by binding to MAS receptor and inhibiting the vasocontraction, angiogenesis and inflammation (Fig. 2)

[106,107].

In addition, Ang (1–7) has showed beneficial effects on hypertensive patients. It also alters renal water retention, and enhances vasodilation [108]. Ang (1–7) suppresses angiogenesis, suggesting that Ang (1–7) can be an endogenous regulator of cell growth. It should be noted that Ang (1–7) reduces VEGF and consequently induces the angiogenesis in xenograft mice model of lung cancer. Altogether, Ang (1–7) reduces the expression of VEGF, placental growth factor (PlGF), HIF-1α and VEGF receptors in human nasopharyngeal carcinoma xenografts in nude mice model. These processes have been further confirmed by *in vitro* studies [109,110]. *In vivo* study on prostate cancer model has showed that Ang (1–7) decreases angiogenesis by reducing the expression of PLGF and VEGF and increasing the expression of fms-like tyrosine kinase-1 (sFlt-1) [111]. Anti-inflammatory functions of Ang (1–7) are induced by binding to MAS receptors on leukocytes [106] Anti-inflammatory and anti-fibrotic activities of Ang (1–7)/Mas are regulated by reducing the leukocyte migration, downregulation of pro-inflammatory cytokines,
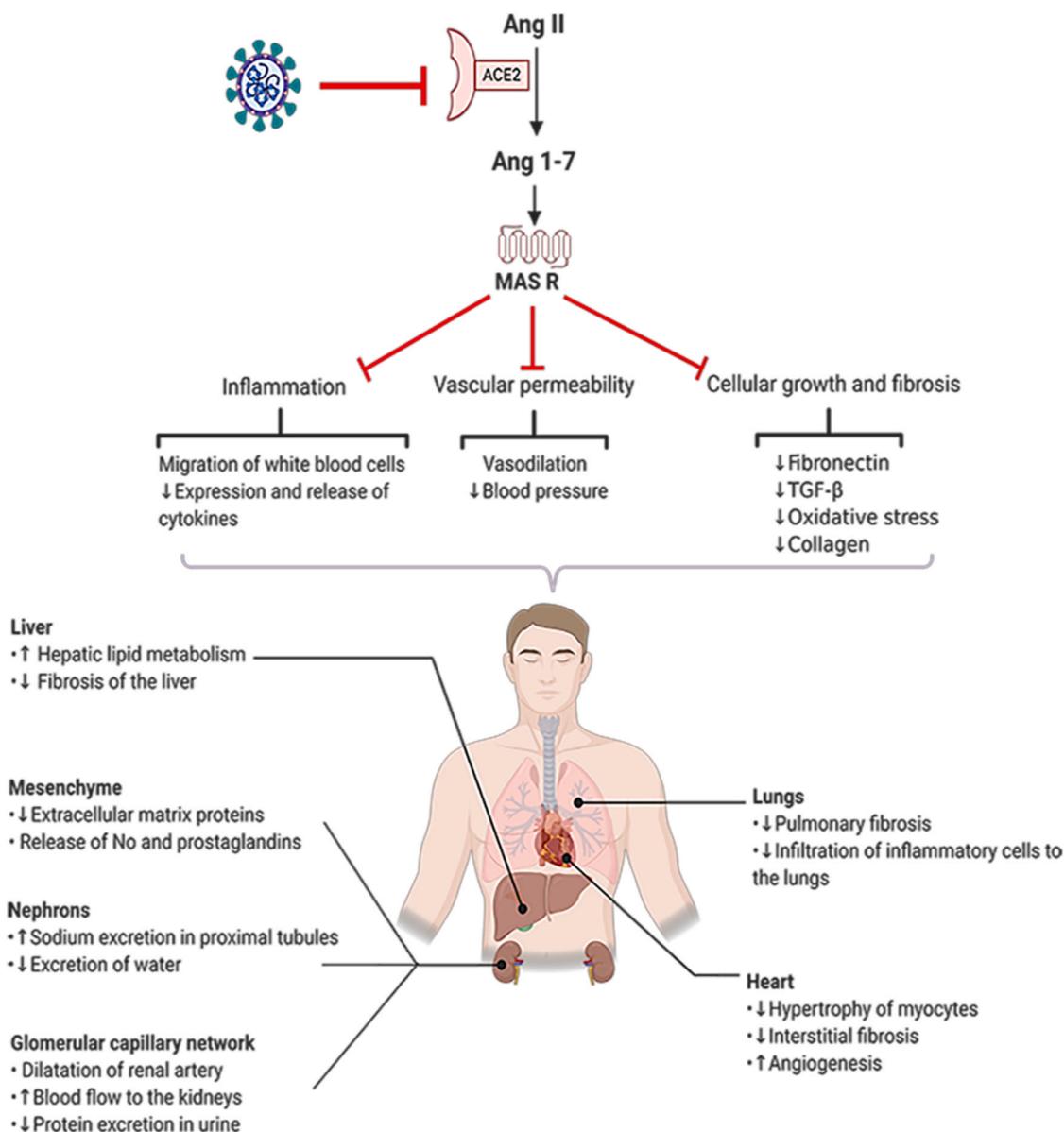
Fig. 2. Ang 1–7 functions in several organs. ACE2 converts Ang II into Ang 1–7 which acts through its receptors (MasR). SARS-CoV-2 downregulates the expression of ACE2 and reduces the concentration of Ang 1–7 leading to progressive deterioration of physiological functions in patients with COVID-19 (Created in BioRender. com). ACE2: angiotensin converting enzyme2, Ang 1–9: Angiotensin 1–9, Ang 1–7: Angiotensin 1–7, MasR: mitochondrial assembly receptor, TGF-β: Transforming growth factor beta.

and reduction of tissue fibrosis factors [106]. In patients with kidney disease, Ang (1–7)/Mas attenuates inflammatory responses by reducing neutrophil influx, downregulating CXC chemokine ligand (CXCL), IL-6, TNF-α, IL-1b, Endothelin-1 (a vasocontractor) and monocyte chemo-attractant protein-1 (MCP-1, a key chemokine responsible for white blood cells migration) [112]. Considering the renal failure in COVID-19 patients, administration of Ang (1–7) might help the recovery of the patients by its anti-inflammatory and anti-fibrotic effects [113]. Ang (1–7) decreases oxidative stress and suppress NF-κB and thus improves permanent middle cerebral artery occlusion [114]. In addition, intra-cerebroventricular administered Ang (1–7) in brain ischemic mice inhibited NF-κB activity which in turn is associated with downregulation of TNF-α, IL-1β and cyclooxygenase-2 (COX-2) and hence could rescue the brain [115]. COVID-19 damages patients' nervous system as virus is able to attack nervous system suggesting the use of Ang (1–7) to reduce the clinical complications [115]. Study on heart tissue (Sprague–Dawley rats) has shown the beneficial role of Ang (1–7) in maintaining the

cardiovascular hemostasis and protection against heart diseases. In heart (Sprague–Dawley rats), Ang (1–7) reduces the expression of in-flammatory cytokines such as TNF-α and IL-6 and increases IL-10 [116]. As ARDS is caused by SARS-CoV-2 infections, Ang (1–7) can be a useful drug candidate for improving lung function. Reduction in the concentration of Ang (1–7) in COVID-19 patients is due to dysregulation, internalization and shedding of ACE2. Ang (1–7) has anti-thrombotic effect by releasing an antithrombotic factor NO via MAS receptor-induced signaling. When concentration of Ang II is low, Ang (1–7) binds to AT2R and increases the concentration of NO and pros-tacyclin in plasma and these factors facilitate clot formation by acti-vating the platelets [115,117–120].

Considering the anti-inflammatory and anti-hypertensive roles and stimulatory effect on clot formation, Ang (1–7) might be beneficial for COVID-19 patients to protect them against thrombosis (Fig. 2).

5. Ang (1–9)

Ang (1–9) is produced from Ang II in a reaction catalyzed by ACE2 or catepsin A [121]. Ang (1–9) binds to AT2R, inhibits the Ang II-AT1R signaling axis [122] and balances the vasoconstrictive/proliferative to vasodilatory/antiproliferative axis and consequently, improves cardiovascular conditions [123]. AT2R-derived signaling functions in cell differentiation, vasodilation and reduces the cell proliferation, inflammation and fibrosis [124].

During post-myocardial infarction, Ang (1–9) improves cardiovascular conditions and left ventricular systolic performance [124–126]. In cardiomyocytes, similar to Ang (1–7), Ang (1–9) exerts positive inotropic effects by increasing calcium transient amplitude and contraction force, and anti-ventricular hypertrophy effect, *in vivo* and *in vitro* (in animal models) [124]. Ang (1–9) reduces blood pressure by affecting endothelial cells [127]. The vascular enhancement is attributed to the release of NO and arachidonic acid in endothelial cells, which improves bradykinin-induced endothelial repair (*in vitro* study on human right atrial and left ventricular tissues) [128]. Ang (1–9) also reduces tissue fibrosis especially in the heart and the lungs [122,129]. Pulmonary fibrosis has been demonstrated in COVOD-19 patients [130], suggesting that Ang (1–9) might be a potential treatment for lung fibrosis. SA Cha et al. have shown that Ang (1–9) downregulates the expression of proinflammatory cytokines such as IL-6, IL-1β, TNF-α, MCP-1 in pulmonary arterial in monocrotaline (MCT)-induced pulmonary hypertensive rats [131]. Furthermore, Ang (1–9) downregulates

proinflammatory cytokines such as IL-6, IL-1β, TNF-α, MCP-1 in pulmonary arterial hypertension in rat model [131]. In hypertensive rats, Ang (1–9) affects heart, aortic wall, and kidney independent of AR2R [132] Therefore, it is anticipated that Ang (1–9) synergizes Ang (1–7) and suppresses the inflammation in COVID-19 patients. Low level of Ang (1–9) and the consequent complications can be attributed to downregulation of ACE2 (Fig. 3).

6. Apelin (1–13)

Apelin (1–13) is a member of apelin family, named after first extraction from bovine stomach extract. This peptide acts as a ligand for previously-identified GPCR AR (APJ) receptors. Apelin in mammalian has 77 amino acids and is engaged to the production of several peptides with various lengths (12, 13, 17 and 36 residues in length) [133,134].

It is the second catalytic substrate for ACE2 with the powerful positive inotropic actions [133]. The isoforms can be generated by the processing enzymes. Apelin-13 is converted to Pyr-apelin-13 by spontaneous rotation of N-terminal glutamine which produces a more stable isoform with higher half-life [134–138].

Apelin-13 is the most abundant isoform in plasma, heart and brain [134]. Apelin and its receptor APJ are expressed in CNS, cardiovascular, circulation, digestive and reproductive systems, fat tissue and skeletal muscles [139,140].

It seems that the main physiological role of apelin is the vascular tone and cardiac contraction modulation [139,140]. In rat model, apelins
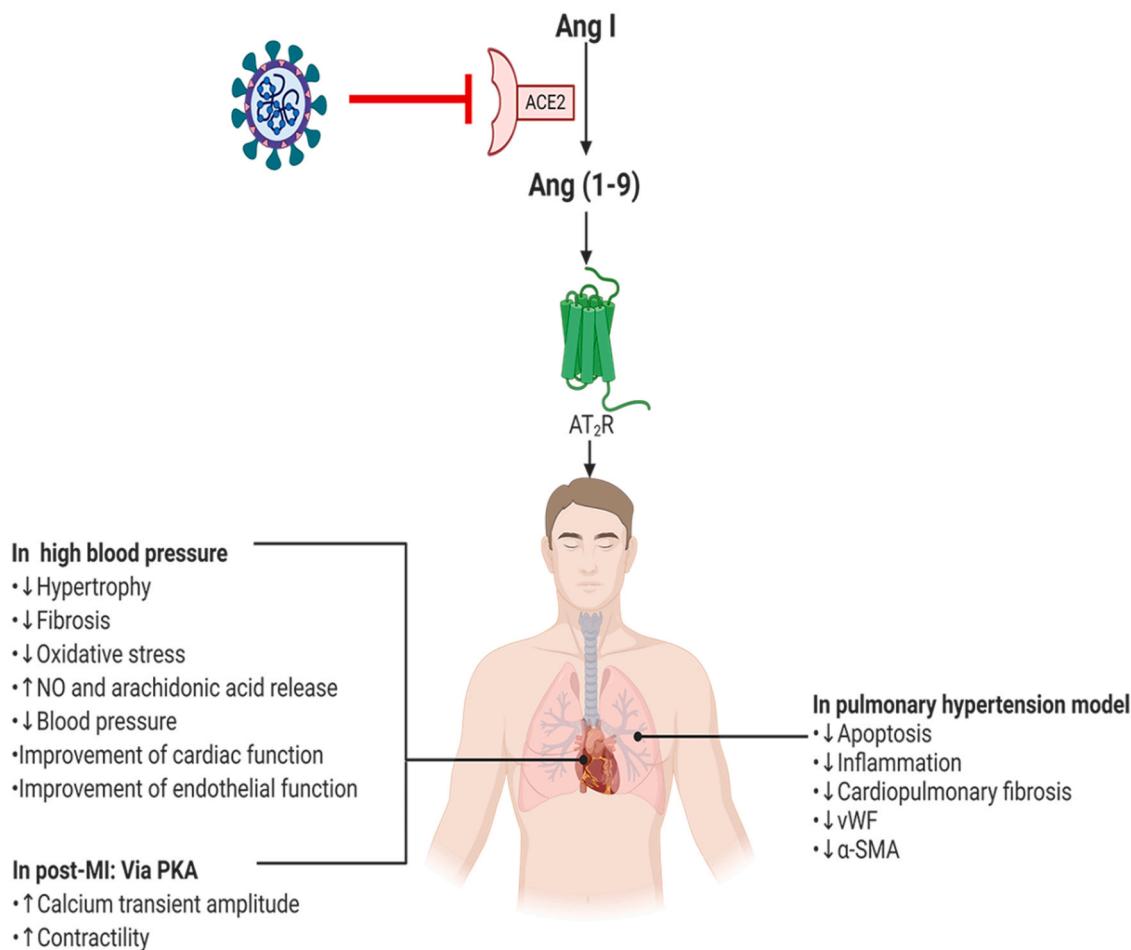
Fig. 3. Ang 1–9 functions in human organs. ACE2 converts Ang1 to the Ang 1–9 and the latter acts through its receptor (AT2R). SARS-CoV-2 downregulates the expression of ACE2 which ultimately reduces the concentration of Ang 1–9. The decrease in the concentration of Ang 1–9 results in the loss of its beneficial functions in several organs in patients with COVID-19 (Created in BioRender.com). ACE2: angiotensin converting enzyme2, Ang I: Angiotensin I, Ang 1–9: Angiotensin 1–9, AT₂R; Angiotensin II receptor type 2, MI: myocardial infarction, vWF: von Willebrand factor, α-SMA: α-smooth muscle actin.

modulate cardiocontraction and vascular tone likely via activation of protein kinase Cε (PKCε) and ERK1/2 signaling pathway [141]. In addition, it has been suggested that apelin upregulates VEGFA, VEGFR2 (kdr Kinase Insert Domain Receptor), angiopoetin-1, Tie2 and endothelial nitric oxide synthase (eNOS) as angiogenic and antifibrotic factors to target the heart (in rat model of post-MI) [142]. Apelin (1–13) also plays anti-apoptotic roles via phosphatidylinositol-3-kinase (PI3K)/Akt, ERK1/2, caspase signaling and autophagy [143]. Hypoxia induces the expression of apelin via HIF-1α-mediated mechanism in smooth muscle cells in the lungs [144].

Moreover, expression of apelin is induced both directly and indirectly by hypoxia and VGEF in endothelial cells respectively [144,145]. Owing to ACE2 downregulation [21,22], apelin-13 might be increased in the plasma of patients with COVID-19. Upregulations of HIF-1α, VEGF and VEGFR2 and activation of eNOS-generating signaling pathway (AMPK and PI3K / Akt) and angiogenesis are induced by apelin (1–13). VEGF, one of the most important growth factors required for angiogenesis, binds to kdr receptor, induces migration and replication of endothelial cells and inhibits the apoptosis. NO produced during downstream signaling contributes to migration, proliferation, and anti-apoptotic function of endothelial cells, stimulates the proliferation of endothelial cells and prevents vascular degeneration. Furthermore, apelin (1–13) has been reported to induce angiogenesis in heart, retina and lungs [146–150].

Similar to Ang II accumulation, increased angiogenesis in COVID-19 patients [8] is probably correlated to the level of apelin. Based on the previous research, during oxidative stress, apelin (1–13) increases antioxidant scavengers and reduces mitochondrial ROS [151–154].

As COVID-19 is a severe respiratory disease, it is hypothesized that apelin-13 is increased in the plasma of the patients with COVID-19. Some studies have shown that administration of apelin (1–13) inhibits NF-κB pathway which reduces proinflammatory cytokines IL-6 E, TNF-α and IL-1β [154,155].

Moreover, LPS-treated mice showed that apelin (1–13) prevents the nuclear migration of NF-κB 65P and subsequently inhibits the NF-κB signaling and the macrophage infiltration [154].

Interestingly, apelin (1–13) prevents the activation of LPS-induced NLR family pyrin domain containing 3 (NLRP3) inflammation in mice lungs and hence reduces the inflammatory cytokines [152,154]. It can be imagined that due to the low half-life, anti-inflammatory and anti-oxidant properties, endogenous apelin (1–13) is not quite stable.

One of the most remarkable roles of apelin (1–13) is to regulate blood pressure. It has been found that APJ receptor interacts with AT1R to decrease the affinity of Ang II binding to AT1R. Therefore, it acts as a negative allosteric regulator for AT1 and negatively regulates Ang II function during hypertension [156]. Moreover, apelin upregulates the expression of ACE2 and reduces the concentration of Ang II (in vitro *and in vivo* studies: in mice) [157,158].

Studies on the administration of apelin, to compare the effects of apelin (1–12), apelin (1–13) and apelin (1–36) on arterial pressure, showed that apelin (1–12) is most potent for arterial pressure reduction in anesthetized mice [159]. Therefore, it is hypothesized that downregulation of ACE2 by SARS-CoV-2 in COVID-19 patients can reduce Apelin (1–12), the product of ACE2. Considering the low half-life of apelin (1–13), it might be accumulated in body upon the entery of SARS-CoV-2 into the cells (Table 2).

7. Apelin (1–12)

Hydrolysis of phenylalanine residue at the C-terminal decreases the half-life of apelin (1–13) in the circulation resulting in the production of apelin (1–12) [157]. Removal of phenylalanine from apelin (1–13) reduces the affinity of the produced apelin (1–12) to APJ receptor three times without significantly changing the biological activity [160].

Tatemoto et al. have shown that in rat model the biological activity of apelin is inversely related to the length of the peptide and therefore, apelin-12 is a highly active isoform [159]. However, the length of at least 12 residues seems to be essential for the biological activity of the apelin derivatives because apleins with 9, 10 and 11 residues are biologically inactive. The half-life of apelin (1–12) in human plasma is 10–15 min [161] while it is about 3 and 8 min for apelin (1–13) in rats [162] and humans plasma [163], respectively. Apelin knockout mice showed hypertension and age-related impaired ventricular contraction similar to the cardiac phenotype of ACE2 knockout mice [164].

Table 2
Some disease-related functions of apelin-13 and APJ.

Organ	Diseases	Experiment model	Effects	Outcomes	Ref
Lung	Pulmonary hypertension (PAH)	Mice, human lung tissues and pulmonary artery endothelial cells	miR[1]424/503 overexpression, FGF[2] and FGFR1[3] downregulation	pulmonary and vascular homeostasis	[232, 233]
	Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)	Mice	Suppression of nuclear translocation and activation NF-κB[4], ↓NLRP3[5], ↓Inflammasome-induced inflammatory responses, ↓ROS[6] production, Mitochondrial apoptosis.	Cytoprotective effects	[154]
	Bronchopulmonary dysplasia	Rat	↓ Fibrin deposition and inflammation.	Reduction of pulmonary fibrosis.	[234]
Heart	Cardiac fibrosis	Mouse and neonatal cardiac fibroblasts	↓ Collagen production, ↓CTGF[7] and ↓TGF-β[8].	Increased cardiac fibrosis.	[235]
	Chronic Heart failure	Human	↑ Peripheral and coronary vasodilatation.	Increased cardiac output.	[236]
Kidney	Diabetic nephropathy	Mice and mesangial cells	↓glomerular filtration rate. ↓ Proteinuria, ↓ glomerular hypertrophy, ↓mesangial expansion and renal inflammation and inhibition of histone hyperacetylation.	Suppression of the development of nephropathy via regulation of histone acetylation.	[237]
	Chronic kidney disease	Mice and HK-2 cells	Antagonist of the TGF-β1/Smad[9] pathway. ↓matrix collagen production and improved tubulointerstitial lesions.	Retardation of CKD progression.	[238]
Brain	Cerebral I/R injury	Rat and neurons cells	Activation of Gαi/Gαq-CK2[10] signaling attenuates eIF2[11]-ATF4[12]-CHOP[13]-mediated neuronal apoptosis.	Protection of neurons against I/R injury-induced apoptosis, facilitation of post-stroke recovery	[239]
	Parkinson's disease	Human neuroblastoma SH-SY5Y cell	↓ ROS and the inhibition of caspase-3 and release of cytochrome c	Protective effects against dopaminergic neural toxicity by antioxidant and antiapoptotic properties.	[240]

1: microRNA, 2: Fibroblast growth factors, 3: Fibroblast growth factor receptors, 4: Nuclear factor kappa B, 5: NLR family pyrin domain containing 3, 6: Reactive oxygen species, 7: Connective tissue growth factor, 8: Transforming growth factor beta, 9: Mothers against decapentaplegic homolog 4, 10: Casein kinase II, 11: Eukaryotic initiation factor 2, 12: Activating transcription factor 4, 13: C/EBP homologous protein.

Apparently, stable responses following apelin (1–13) injection is due to ACE2-induced apelin (1–13) cleavage and the production of apelin (1–12). Studies on rats with coronary artery occlusion have shown the apelin (1–12) in heart which reduced the mean arterial pressure [165]. Apelin (1–12) injection following local ischemia ameliorates myocard infarction and damage to heart membrane in rats [166].

In humans, apelin (1–12) increases blood pressure in a dose-dependent manner. Apelin (1–12) induces the overexpression of ACE2 [158]. On the other hand, SARS-CoV-2 infection is associated with a downregulation of ACE2 expression [21]. Therefore, it has been suggested that induction of the expression of ACE2 particularly apelin (1–12), would lead to increase in the concentrations of Ang (1–7) and Ang (1–9) which in turn might promote the recovery from COVID-19. Since acute cardiac injury is among the most common complications in COVID-19 [167], apelin (1–12) reduction may induce cardiac injury as it normally plays protective roles in heart tissue (Table 3). This reduction also causes cardiovascular failure, as it reduces systemic oxygenation during pneumonia and activates T cells and immune signaling [168]. Downregulation of ACE2 in COVID-19 might attenuate the immune response to SARS-CoV-2 due to decrease in the concentration of apelin (1–12) which can explain cardiac injury by taking into account the protective role of apelin (1–12) for heart tissue. It is crucial to investigate the effects of Apelin (1–12) and Apelin (1–13) on the repair of endothelial cells as immunoreactivity of [Pyr1] apelin-13 (1–12)-like has been discovered in neighboring endothelial cells [161].

8. Dynorphins A (1–13) and (1–12)

Dynorphins (endogenous opioid neuropeptides) are the ACE2 substrates with pain relieving effects [169,170].

Dynorphins binds to κ-opioid receptors and act as inhibitory neurotransmitters and induce pain desensitization [171]. Dynorphin A (1–13) is a breakdown product of dynorphin A which is synthesized as pre-prodynorphin [172]. Apart from pain relieving roles, high concentration of dynorphins can induce hyperalgesia and allodynia or even the production of neurodegeneration metabolites [173].

and dynorphin A3–13 reduce rat spinal cord blood flow by non-opioid mechanisms. Brain research. 1987;436(2)Intrathecal injection of dynorphins into rat subarachnoid causes persistent flaccid paralysis of hindlimbs and loss of pain response [173]. Dynorphin A (1–13) acts via NMDA-glutamatergic and κ-opioid receptors [174]. It also affects neuron survival so that the toxic effects of dynorphin on the neurons are mediated by glutamatergic receptors, because high concentrations of dynorphin A (1–13) (μM) can activate NMDA receptors which in turn increase intracellular concentration of Ca^{2+} and kill many neuron cells (Fig. 4) [175]. Neurological complications were common in patients with Covid-19 who were hospitalized for treatment in Wuhan [176–178]. Considering the destructive effects of dynorphins

accumulation [21], the plasma concentration of dynorphin A (1–13) in COVID-19 patients might be increased due to ACE2 downregulation which can induce brain neurotoxic effect. Thus, dysregulation of ACE2 after SARS-CoV-2 entry and consequent accumulation of dynorphin A (1–13) versus decreased concentration of dynorphin A (1–12) (1–13) [179] might be of the causes of the loss of taste and smell in COVID-19 patients due to the neurotoxic effects of dynorphin A. Furthermore, a study has shown that immune cells secrete dynorphin A and also IL-1 can induce the production of dynorphin A from these cells (in the rat model of localized hindpaw inflammation) [180]. Since IL-1 is increased in COVID-19 patients [181], it is thought that production of dynorphin A might be increased more in COVID-19.

Finally, dynorphin A (1–12) is produced by the cleavage of dynorphin A (1–13) by ACE2 [170,182]. Dynorphin A (1–12) is one of the main metabolites of dynorphin A (1–13) in human CSF and plasma which binds to κ-opioid receptor with the less affinity than dynorphin A (1–13) [183,184]. In human blood half-life of dynorphin A (1–12) is 1.9 min (more than dynorphin A1–13, half life: 0.9 min) [185]. It is anticipated that its accumulation shows only mild side effects, ACE2 dysregulation induced by the entry of SARS-CoV-2 into the cells decreases the concentration of dynorphin A (1–12) and might lead to loss of its counterbalancing effects against accumulated dynorphin A (1–13).

9. Link between immune responses and renin-angiotensin system (RAS)

Adoptive and innate immunities play a key role against SARS-CoV-2, however, the virus can induce hyperinflamation or cytokine storm [57]. Although different factors induce cytokine storm, studying the dysregulation of ACE2 and correlation with immune responses seems interesting (Fig. 5). A previously-published study has reported that downregulation of ACE2 in macrophages in COVID-19 patients increases the inflammatory cytokine and production of NO. On the other hand, Ang II induces cell proliferation and cytokine production implying the role of Ang II in regulating the cell signaling in inflammation and immune-related diseases [186]. IL-2 is an immune cytokine that stimulates the proliferation of T cells [187]. Studies on Jurkat T-cells showed that Ang II-ATR1-ERK axis activates lymphocyte T and leads to production of IL-2 [186]. For instance, AT1R found on the surfaces of various immune cell and T cells contains endogenous RAS and thus express renin, renin receptor, angiotensinogen and ACE2 [188]. Ang II-AT1R axis in T cells regulates activation of T lymphocytes and secretion of IL-2, IFN-γ and reduces IL-4 [189,190]. The axis also induces differentiation of Th0 to Th1 cell through activation of AT1R-PKA-proteasome pathway [191]. Th1 is responsible for the production of IL-1B, IFNγ, CXCL10, and CCL2 [192]. In human Jurkat T cells (*in vitro* study), Apelin-APJ system upregulates the expression of CD69 and CD25 on the surface of T lymphocytes and stimulates the cells

Table 3
Disease-related effects and outcomes of the administration of apelin-12.

Organ	Diseases	Experiment model	Effects	Outcomes	Ref
Heart	Conscious rat	Rat	↓Mean arterial pressure and ↑ heart rate	Arterial and venous dilator	[241]
	Hypertension	Rat	↓Systolic and diastolic blood pressure	Hypotension	[242]
	Failing rat cardiac muscle	Rat	↑ Transients [Ca2+]I and ↑ force development	Selective positive inotropic effect	[243]
	Cardiac I/R[5] injury	Rat	Mediating PLC[1] and survival kinases, PKC[2], PI3K[3], and MEK[4]1/2 signaling pathways with activation of downstream targets, NO synthase and mito K ATP channels, and sarcolemmal Na+/H+ and Na^+/Ca^{2+} exchangers.	Reduction of irreversible cardiomyocyte damage, improvement of cardiac dysfunction, enhancement of metabolic restoration and membrane integrity.	[244]
Brain	Cerebral infarction	Mice	Improvement of the neurobehavioral score and brain edema. Inhibition of the morphological changes and apoptosis of neuronal cells, Activation of caspase-3. ↑ Bcl[6]-2. ↓Bax[7], ↓caspase-3, ↓p-JNK[8] and p-p38[9]	Inhibition of the JNK and P38/MAPK[10] signaling pathway. protection to neurons	[245]

1: Phospholipase C, 2: Protein kinase C, 3: Phosphatidylinositol 3-kinase, 4: Mitogen-activated protein kinase, 5: Ischemia/reperfusion, 6: B-cell lymphoma 2, 7: B-cell lymphoma protein 2 -associated X, 8: C-Jun N-terminal kinase, 9: Phosphorylated p38, 10: Mitogen-activated protein kinase.
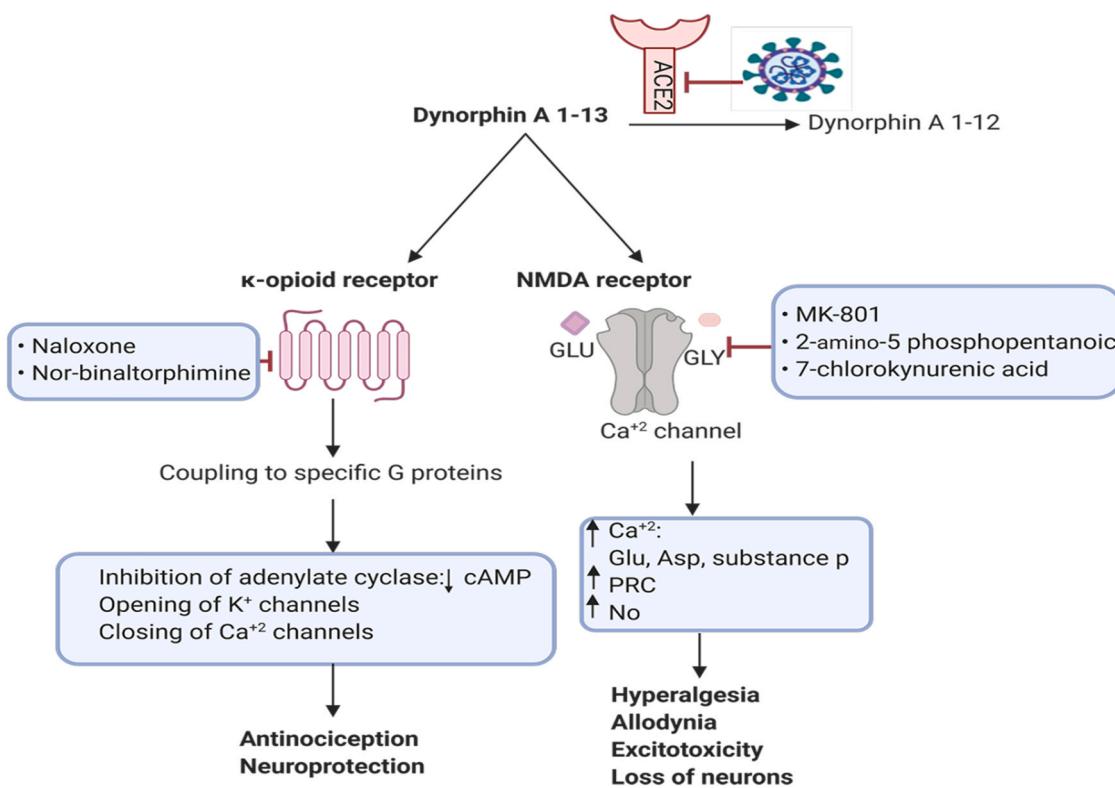
Fig. 4. The binding of dynorphin-13 to κ-opioid and NMDA receptors. Dynorphin A (1–13) binds to κ-opioid receptor and NMDA-glutamatergic. ACE2 degrades dynorphin A 1–13 and subsequently produces dynorphin A 1–12. SARS-CoV-2 downregulates the expression of ACE2 and thus the harmful effects of dynorphin A 1–13 accumulation causes the loss of neurons via NMDA receptor (Created in BioRender.com). PKC: Protein kinase C, NO: nitric oxide, cAMP: Cyclic Adenosine Monophosphate, NMDA: N-Methyl-D-aspartic acid.

proliferation and activity [193]. Apelin (1–13) suppresses IFN-γ, IL-2 and IL-4 in activated T lymphocytes in mice [194]. AT1R is also expressed on macrophages when monocytes are differentiated to macrophages [195] and upregulates inflammatory cytokines such as TNF-α, IL-1b, IL-6, and IL-10 and produces ROS through NF-κB and AP-1 pathway [196]. Apelin (1–13) promotes growth and differentiation of macrophages by binding to APJ through ERK1/2 and mitogen-activated protein (MAP) kinase pathways and by inhibition of apoptosis [197, 198]. Apelin (1–13) also reduces the production of cytokine and ROS in macrophages and prevents the conversion of macrophage to foam cells [199]. Moreover, dendritic cells express AT1R and hence activate NF-κB for the production of proinflammatory cytokines [200,201].

Studies on DC2.4 cells, a murine bone marrow-derived DC line, showed that Ang II activates dendritic cells in part through p65 / NF-κB and ERK2/1 and STAT1 [202].

Furthermore, dynorphin A induces the secretion of IL-1, TNFα, macrophage-mediated phagocytosis, chemotaxis in mononuclear cells and neutrophils, and reduces the release of NO [203]. The anti-inflammatory functions of Ang (1–9) and Ang (1–7) have been already discussed, however, there is not much information about their functions on immune cells. Ang (1–7) has been shown to induce macrophage-mediated anti-inflammatory responses via MAS axis (in murine models of autoimmune neuroinflammation and atherosclerosis) [204]. AT2R, a receptor for Ang (1–9), was found on T cells and NK cells and anti-inflammatory function of AT2R ligands or agonists is dependent on the formation of epoxyeicosatrienoic acid and direct inhibition of NF-κB inflammatory signaling. In addition, lymphopenia is one of the most informative diagnostic markers of COVID-19 which is produced as a consequence of cytokine storm [205]. The cytokine storm and increased inflammatory cytokines like TNF-α and IL-6 induce apoptosis and necrosis in T cells [206]. In patients with COVID-19, the increased cytokines were correlated to decreased T lymphocytes and according to

the function of Ang II, it is involved in the production of these inflammatory cytokines and acts to reduce lymphocytes [207]. On the other hand, Ang 1–7, Ang 1–9 can be effective as anti-inflammatory substance on preventing the reduction of lymphocytes.

Moreover, pyroptosis, a novel inflammatory form of programmed cell death following infection, is the other cause of lymphopenia induced by SARS-CoV [208].

Pyroptosis is a much faster process than apoptosis and is associated with diffusion of proinflammatory factors [209]. Pathogen-associated molecular patterns (PAMPs) binding to pattern recognition receptors (PRR) such as nitric oxide synthase and NLRP3 on host cells, activate caspase-1, a key component of innate immunity which in turn leads to cell perforation, inflammation, cell lysis and secretion of IL-1β and IL-18 [96]. Similarity between SARS-COV and SARS-COV-2 on one hand and increased IL 1β as a marker for pyroptosis on the other hand suggests that pyroptosis may explain the lymphopenia in COVID-19 patients [92, 118]. It could be initiation of inflammatory signaling induced by increased Ang II as well as pyroptosis-mediated release of cytokines (Fig. 5) [201]. In sum, these conditions can exacerbate the inflammation induced by the imbalance between ACE2 substrates and products in the COVID-19 patients.

10. Conclusion

Considering the key role of ACE2 as a functional receptor for SARS-CoV-2, targeting the receptor to block the virus entry is studying [210]. We suggest that downregulation of ACE2 can be one of the main causes of SARS-CoV-2 symptoms. COVID-19 severity can be changed by reduction in ACE2 products such as Ang (1–7), Ang (1–9), apelin (1–12) and accumulation of substrates such as apelin (1–13) and Ang II [211]. Given the downregulation of ACE2, accumulated apelin (1–13) can stimulate the pulmonary embolism. On the other hand, when the ACE2
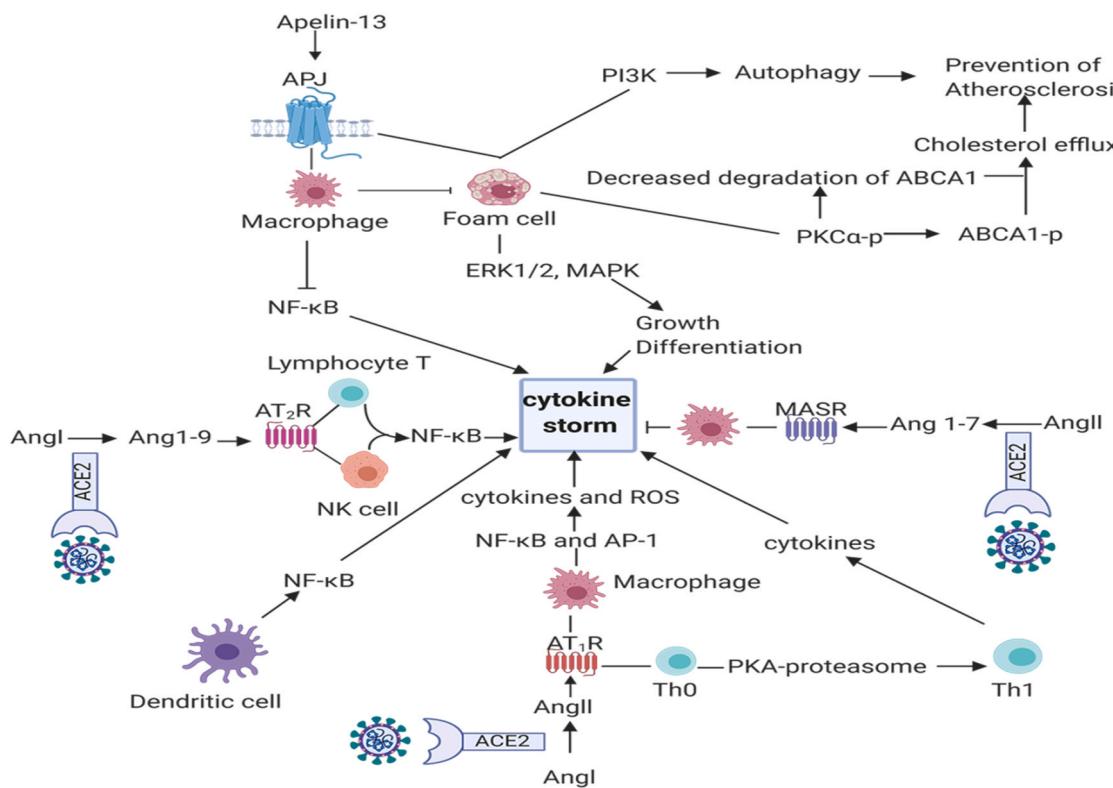
Fig. 5. Schematic presentation of the interactions among the immune system and ACE2 substrates and products (Created in BioRender.com). ACE2: Angiotensin converting enzyme2, Ang I: Angiotensin I, Ang II: Angiotensin II, Ang 1–9: Angiotensin 1–9, Ang 1–7. Angiotensin 1–7, AT1R; Angiotensin II receptor type 1, AT2R; Angiotensin II receptor type 2, MAS R: Mas receptor, APJ: Apelin receptor, ROS: Reactive Oxygen Species, ERK1/2: Extracellular signal-regulated kinases, MAPK: Mitogen-activated protein kinase, PI3K: Phosphatidylinositol-3-kinase, PKC: Protein kinase C, Th1: T helper cell 1, Th0: Naive T cell, NF-κB: Nuclear factor-κB, AP-1: Activator protein 1, ABCA1-p: ATP binding cassette transporter A1- phosphorylated.

is downregulated by SARS-CoV-2, the concentration of apelin (1–12) can be decreased. It is also possible to hypothesize that decrease in the concentration of apelin 1–12 in the plasma of COVID-19 patients may increase the damages of endothelial cells (apelin-12 repairs endothelial cells). However, further studies are required to test these hypotheses. Moreover, higher concentration of apelin (1–13) during severe pulmonary embolism [212], a common complication in COVID-19 and the major cause of death in the patients [213,214], might be suggested as a possible biomarker for diagnosis of the stages of the COVID-19 severity. Losses of taste and smell have also been listed as COVID-19 symptoms which might be due to accumulation of the dynorphin A (1–13). Possible neuronal damage for the losses of taste and smell induced by coronaviruses might be attributed to virus entry into the nervous system and subsequent hypoxia-induced damages following the pulmonary disorders and the production of inflammatory cytokines (cytokine storm) [215–217]. It has been suggested that targeting ACE2 expression can be used as a treatment for COVID-19 and thus, ARB and ACE inhibitors (ACEi) have been used to increase the level of ACE2 but failed to treat [211,218]. It should be noted that ACEi have been already used in asian brain ischemic patients [219] as well as Parkinson disease which questions the negative effects of ACEi [220–223].

Considering the severe thrombotic complications in the COVID-19 patients [224], it has been suggested that the use of anti-coagulants may reduce the symptoms at the expense of serious side effects. Inflammatory responses can play a key role against SARS-CoV-2 by removing the infection, however, hyperinflamation or cytokine storm can lead to death, and thus the use of non-steroidal anti-inflammatory drugs is not a safe and promising therapeutic approach to treat COVID-19. Considering the anti-thrombotic, anti-hypertensive and anti-oxidative stress properties of ACE2 products such as Ang (1–7) and cardiovascular protective function of Ang (1–9), we suggest the use of

the more stable analogs of these compounds to reverse the harmful effects of Ang II accumulation induced by dysregulation of ACE2. As inflammation, vascular failure, blood pressure and von Willebrand factor play roles in vascular thrombosis [225,226], Ang (1–9) might have protective role against vascular thrombosis in COVID-19 patients. In addition, Ang (1–7) may exert more efficient protection against COVID-19 than recombinant soluble ACE2 or AT1 blockers, however this needs to be investigated and clinically evaluated. We also suggest that the administration of apelin (1–12) can be tested for the treatment of the COVID-19 due to prolonged half-life, higher affinity to AT1 and higher expression in endothelial cells. According to the results presented previously, the lack of apelin (1–12) causes the failure of vascular repair and pulmonary embolism and thereby administration of apelin (1–12) may ameliorate the symptoms of COVID-19. Finally, antagonists of dynorphin A (1–12) may reduce the harmful effects of dynorphin A (1–13) accumulation triggered by dysregulation of ACE2 upon virus entry. Nevertheless, these hypotheses should be evaluated and tested as potential therapeutic strategies for COVID-19 treatment.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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