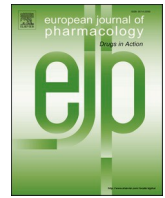




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Review

Association of ACE inhibitors and angiotensin type II blockers with ACE2 overexpression in COVID-19 comorbidities: A pathway-based analytical study

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ABSTRACT

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) outbreak is a major public health concern, which has accounted for >1.7 million deaths across the world. A surge in the case fatality ratio as compared with the infection ratio has been observed in most of the countries. The novel Coronavirus SARS-CoV-2 shares the most common sequence with SARS-CoV, but it has a higher rate of transmission. The SARS-CoV-2 pathogenesis is initiated by the binding of viral spike protein with the target receptor Angiotensin-Converting Enzyme 2 (ACE2) facilitating virus internalization within host cells. SARS-CoV-2 mainly causes alveolar damage ranging from mild to severe clinical respiratory manifestations. Most of the cases have revealed the association of Coronavirus disease with patients having earlier comorbidities like Hypertension, Diabetes mellitus, and Cerebrovascular diseases. Pharmacological investigation of the SARS-Cov-2 patients has revealed the frequent use of drugs belongs to Angiotensin-converting enzyme inhibitors (ACEi) and/or Angiotensin II type I receptor blockers (ARBs). Interestingly, a significant increase in ACE2 expression was noticed in patients routinely treated with the above group of drugs were also reported. To date, the association of ACEi and/or ARBs with the up-regulation of ACE2 expression has not been defined distinctively. The proposed review will focus on the pathways which are responsible for the upregulation of ACE2 and its impact on gravity of SARS-CoV-2 disease.

1. Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) caused Corona Virus Disease 2019 (COVID-19) in more than ~77 million individuals with ~1.7 million fatalities globally. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, with a significant surge in COVID-19 cases reported in most countries. The onset of COVID-19 infection actuates with the migrating of the virus into the respiratory tract and more prominently damaging the alveolar sacs of the respiratory system. SARS-CoV-2 is exceptionally infectious in nature and it spreads through respiratory droplets, thus social distancing has been recommended as a primary preventive measure. The time of incubation for the virus is 1–14 days within the hosts, yet the transmission can result in community spread due to high asymptomatic cases around the world. Statistical analysis has revealed that only 5–10% of the infected individuals show the severe manifestations of COVID-19 disease (Perella et al., 2019; Zhang et al., 2020a; Lai et al., 2020). The mortality of COVID-19 is ~0.2% among young healthy

individuals, while the rate is high in old age people with preexisting hypertension and cardiovascular comorbidities. Moreover, SARS-CoV has a mortality rate of 10% as compared with MERS-CoV having a rate of 35%, but these earlier reported a low transmission rate of the virus Azhar et al., (2019); WHO (https://www.who.int/csr/sars/country/2003_08_15/en). But the Confirmed Fatality Ratio (CFR) of SARS-CoV-2 varies by country from less than 0.1%–28% (WHO/2019-nCoV/Sci_Brief/Mortality/2020.1). Major symptoms of SARS-CoV-2 infection comprise fever, headache, mild chest pain, loss of taste/smell, and breathing problems (Wang et al., 2020). Initial attachment of SARS-CoV-2 with the host cells is facilitated by the attachment of viral spike protein with the angiotensin-converting enzyme 2 (ACE2) receptors. The ACE2 expression pattern differs significantly among various tissues and organs. Thus the susceptibility of cells towards the infection eventually depends on the ease of viral internalization using ACE2 (Zhou et al., 2020). A case study in China on COVID-19 affected population reported a significant clinical history of Diabetes and Cerebrovascular comorbidities within 32 out of 52 patients

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under the Intensive Care Unit (ICU). Likewise, two independent studies on COVID-19 infected population reported the presence of single or multiple comorbidities like Diabetes Mellitus, Hypertension, and Cerebrovascular disease among 1099 patients (Yang et al., 2020; Zhang et al., 2020b). Further, clinical investigation on these groups of patients reported a prolonged use of angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin II type I receptor blockers (ARBs) for medications. Notably, the presence of ACE2 was considerably increased in patients with Type I or II Diabetes mellitus, due administration of ACEi and/or ARBs (Li et al., 2017). Similarly, medication for hypertension with ACEi and ARBs leads to abundant ACE2 expression (Wan et al., 2020). Earlier, a report has suggested the use of ARBs like Olmesartan may defend cardiovascular rearrangement by heart cardiac nitric oxide and accumulation of angiotensin-(1–7) mediated by high expression of ACE2 (Agata et al., 2006). Thus continuous use of ACEi and ARBs to treat the comorbidities leads to the overexpression of ACE2 was clearly reported in many instances, but not properly analyzed. Hence, we have attempted to analyze the plausible pathways relevant to the question in the form of review literature.

2. SARS-COV-2 proteome characteristics

The SARS-CoV-2 genome (~30 Kb) encodes for ORFs and divided into three parts based on the structural and functional roles in pathogenesis. Major portion of the genome codes for 16 non-structural proteins (nsp 1-16) which forms the replicase complex. One third of the SARS-CoV-2 genome codes for accessory (3a, 3 b, 6, 7a, 7 b, 8a, 8 b, 9 b, 9c) and four major structural (Spike, Envelope, Membrane, and Nucleocapsid) proteins (Lu et al., 2019; Zhang et al., 2020c). Among them, Spike protein (S) mainly facilitates the attachment with the host cells (Perlman and Netland, 2009). The size of Spike protein ranges between 180 and 200 kDa bearing an extracellular transmembrane and intracellular C-terminal domains (Bosch et al., 2003). Spike protein has 1273 residues with a major distribution of amino acids in the S1 and S2 subunit; The S1 subunit mainly comprises one N-terminal region (14–305) followed by the receptor-binding domain (319–541). S1/S2 subunit of the Spike proteins attaches to the ACE2 receptors and facilitate the formation of endosomes. Further, the S2 subunit covers the region of fusion peptide (788–806), transmembrane domain (1213–1237), and cytoplasmic domain (1237–1273) (Xia et al., 2020). Both subunits (S1 and S2) together shape the head and stalk structure of Spike protein (Tang et al., 2020).

2.1. ACE2 receptor and SARS-Cov-2 spike protein interactions

Spike protein of SARS-CoV-2 binds with human ACE2 receptors with higher affinity than the S proteins of SARS-CoV (2003). During infection, the S protein interacts with ACE2 through the receptor-binding domain of S1 subunit, facilitating the protein interaction with the host cells for viral attachment and pathogenesis. The high-affinity binding between Spike protein and ACE2 induces a three dimensional rearrangement in the Spike protein, followed by the splitting of the S1/S2 poly basic site by Cathepsin L protease (Wrapp et al., 2020; Wu et al., 2020; Liu et al., 2020). ACE2 mediated SARS-CoV-2 internalization within the host cell is the primary stage of virus infection, but it also requires the type II transmembrane serine protease (TMPRSS2) for the activity of the viral spike protein [21]. Clinical investigations confirmed the potential application of Camostat Mesylate (protease inhibitor) for TMPRSS2 in restricting the virus internalization and acting against SARS-CoV-2 infection (Hoffmann et al., 2020; Matsuyama et al., 2020). ACE2 acts against the actions of ACE by metabolizing its catalytic fibrogenic peptide AngII (angiotensin II) into Ang (1–7). Wang et al. studied the expression pattern for ACE2 through the analysis of genes in the specific tissues; standard range for the expression (–10 to 5). Mild to moderate expression (0–5) was observed in every tissue, but specifically higher expression (average to maximum limit; log₂-transform) was in the blood

vessel, lungs, ovary, adipose tissue, heart, small intestine, etc (Li et al., 2020). Under comorbid conditions like diabetes, cardiovascular diseases, and cancer, the ACE2 overexpression may balance the detrimental effects of the Angiotensin-II mediated AT1R signaling pathway. Further, studies revealed the abundance of ACE2 in type II alveolar cells and enterocytes, thus facilitating accelerated SARS-CoV-2 multiplication causing severe alveolar damage (Hamming et al., 2004; Turner et al., 2004). Thus, ACE2 acts as a key player in the SARS-CoV-2 pathogenesis on the basis of structural compatibility, stable interaction, and high-affinity binding.

3. Role of ACE2 in the regulation of Renin-angiotensin system

Renin-Angiotensin System (RAS), a hormonal system that controls blood pressure, electrolyte, and volaemia is regulated by the classical angiotensin-converting-enzyme I (ACE1). Later, a homolog of ACE1 was recognized as angiotensin-converting enzyme 2 (ACE2) a carboxypeptidase that is vital for regulating cardiovascular homeostasis (Patel et al., 2012). It forms ang 1–9, ang 1–7 from angiotensin I and angiotensin II respectively (Donoghue et al., 2000). Further it controls the vasodilatation and reduces the hypertrophic effects (Tipnis et al., 2000). In counter-regulation, it cleaves the C-terminal residues from kinetensin, neurotensin, and des-Arg bradykinin peptides but remains ineffective against bradykinin (Vickers et al., 2000). ACE2 also cleaves peptides casomorphins, dynorphin A and apelins (Wang et al., 2016). The RAS system comprises two counter-regulatory mechanisms mediated by ACE, angiotensin type 1 (AT1R), ang II and ACE2, ang (1–7), angiotensin type 2 (AT2R) receptors followed by Mas receptor (MasR). (Fig. 1). The classical enzyme ACE catalyze angiotensin I to angiotensin II which acts like some agonist in mediating vasoconstrictive and pro-inflammatory effects through AT1R. Angiotensin II acts on both AT1R and AT2R as part of the counter-regulatory mechanism, to maintain a proper balance between vasoconstriction and vasodilation in addition to other physiological roles. Angiotensin (Ang I) is degraded by the ACE to form Ang II a substrate for ACE2 (homolog of ACE). The major role of ACE2 is the depletion of Ang II which led the way for the emergence of angiotensin 1-7 to counter the effects of Ang II within the RAS system (Tikellis and Thomas, 2000; Mercure et al., 2008; Oudit and Penninger, 2011). Thus, ACE/Ang I and ACE2/ang 1–7 combos are part of the RAS system, and elevated ACE2 levels are shown to prevent heart failure, diabetes, and hypertension. The above findings confirm the pro-inflammatory activity of ACE2 along with Ang II-mediated AT1R signaling is proved as vital in the RAS system (Alenina et al., 2008; Bader, 2013). The entire RAS system is regulated by AT1R, AT2R, and MasR receptors. AT1R acts as a receptor for the regulation of anti-diuresis and vasoconstriction. But, AT2R and MasR both promote diuresis and vasodilatation. Moreover, MasR was shown to exhibit similar effects of AT2R and attenuates AT1R mediated signaling (Sampaio et al., 2007; Santos et al., 2007; Tallant et al., 2005; Zhang et al., 2014). In comparison, with the downstream signaling pathway of the ACE/Angiotensin II-mediated AT1R axis, the ACE2/Angiotensin 1–7/MasR and ACE2/Angiotensin 1–9/AT2R axis were reported as a physiological regulator against the former axis in activating and balancing the RAS system (Oudit et al. 2003, 2007; Lo et al., 2013; Danilczyk and Penninger, 2006). Based on the reports, ACE2 was determined not only to regulate the RAS system but also to limit the activity of Angiotensin II and ACE.

4. ACEi and ARBs association with the ACE2 overexpression

ACE2 is the predominant regulator against increased vasoconstriction and pro-inflammatory responses induced by angiotensin II type 1 receptor axis. Based on ACE2 abundance in COVID-19 infected people, several studies have suggested the risk of developing COVID-19 with the administration of ACEi and ARBs as indirectly this therapeutics over produce the circulating ACE2 transcripts in the cells (Zheng et al., 2020; Fang et al., 2020; Watkins, 2020). Few studies have somehow suggested

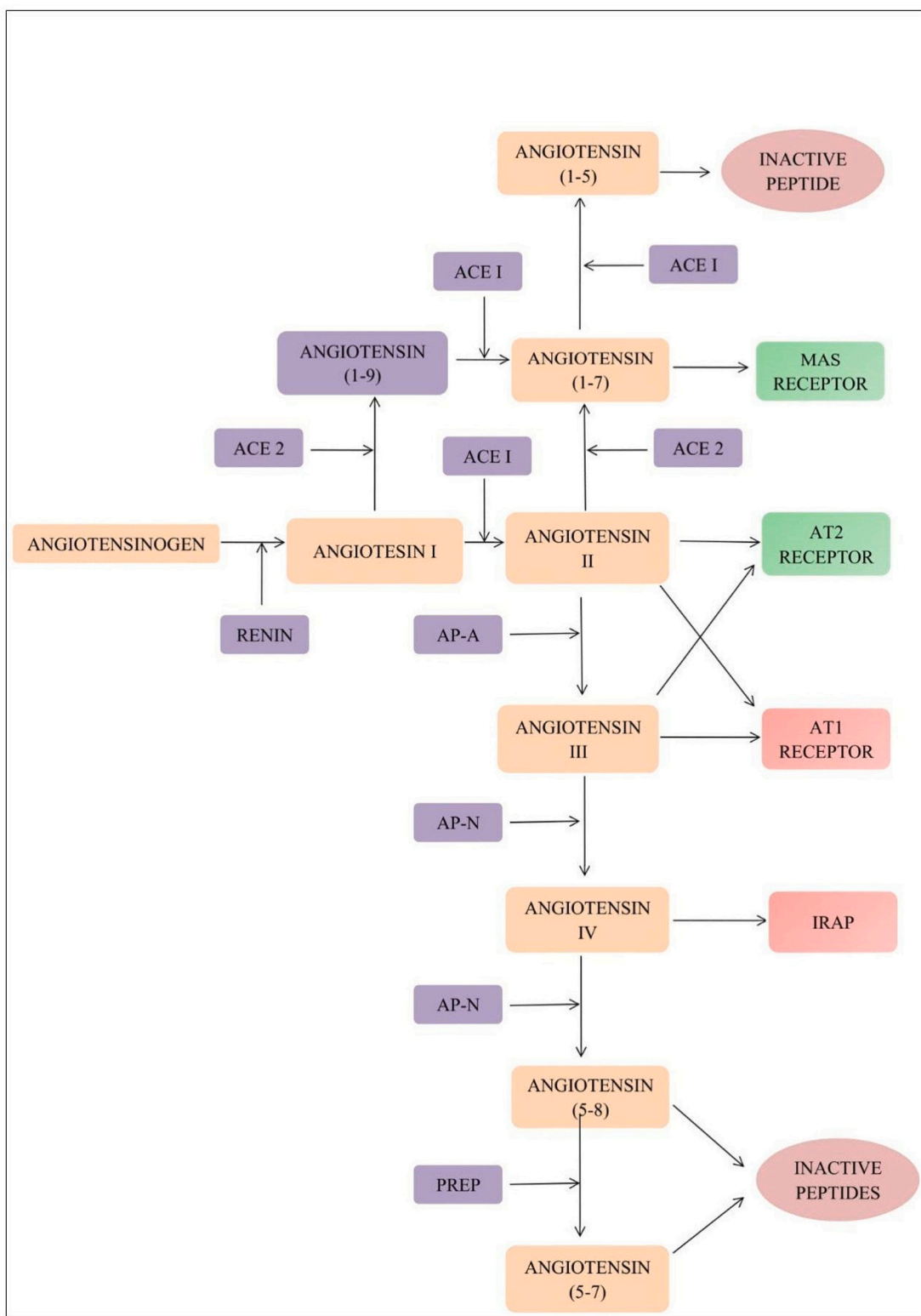


Fig. 1. Diagrammatic portrayal of the Renin-angiotensin system. (AP-A: Glutamyl aminopeptidase, AP-N: Alanyl aminopeptidase, PREP: Prolyl endopeptidase, IRAP: Leucyl and cystinyl aminopeptidase).

the risk of ACEi and ARBs with the development of ACE2 over-expression, but the evidence for approving alternative pharmacological agents over these inhibitors or blockers is still lacking and requires more clinical interventions. Salim S. Al-Rejaie et al. reported that the drug captopril (ACEi family drug) can regulate ACE2 overexpression while

downregulating the angiotensin II-dependent AT1 receptor downstream signaling and RANKL expression in osteoporotic rats. The expression of ACE2 was considerably upregulated in comparison with classical ACE expression. Thus, captopril demonstrated a clinical role in the upregulation of the ACE2 dependent Mas receptor signaling cascade in

restoring bone metabolism (Esler and Esler, 2020). The therapeutic application of captopril in treating hypertension and cardiovascular comorbidities exhibited positive clinical outcomes. Similarly, Enalapril a known ACEi was reported to increase ACE2 expression in the kidney tissues whereas no such significant fold change was observed in TMPRSS2 mRNA expression (Abuhashish et al., 2017; Saheb et al., 2020). Chappell and his group has reported increased expression of ACE2 mRNA, while optimum reduction in angiotensin II (plasma) expression upon treating the cardiac cells with lisinopril and losartan (Ferrario et al., 2005). A significant change was not observed in the cardiac ACE2 activity by the combination of both drugs. In the case of diabetes, renal ACE2 transcript levels were found to be bountiful after the administration of Losartan. Jessup JA et al. has characterized the ACE2 mRNA found within the heart and kidney of Losartan-treated transgenic rats (Jessup et al., 2006). ACEi and ARBs are individually used as medication for type II diabetes, but dual drug combined therapy can also auto-regulate the ACE2 expression. Further, the *in vivo* animal model study revealed a plausible association of ACE2 overexpression concerning anti-diabetic medication. Insulin administration in type I and II diabetes mellitus attenuates renal disintegrin and metalloproteinase domain 17 (ADAM-17) activities. ADAM-17 regulates ACE2 inactivation by cleaving off the ACE2 enzyme, but the reduced activity of ADAM-17 can also lead to an upregulated expression of ACE2. The overexpression of ACE2 in heart and lungs of the diabetic animal model was analyzed with Liraglutide administration (Wysocki et al., 2006; Xye-Ying and Jing Bo, 2016). Apart from ACE inhibitors and ARBs, thiazolidinediones also act as a vasodilator. Generally, ACE2 levels are elevated due to the intake of antidiabetic drugs. Similarly, higher expression of ACE2 was also found among the Insulin administered animal models. Miller HD et al. has described the relationship between ACE2 upregulation and administration of glucagon-like peptide 1 (GLP) agonist or dipeptidyl peptidase-4 (DPP) inhibitors to treat diabetes (Dambha-Miller et al., 2020). Further, type 2 antidiabetic drug thiazolidinedione was also reported to up-regulate ACE2 expression *In vivo* and *In vitro* models (Dambha-Miller et al., 2020). Thiazolidinediones improve vasodilation in diabetic patients by regulating the signaling cascade linking peroxisome proliferator-activated receptor-gamma (PPAR γ) and Renin-Angiotensin System (Sarafidis et al., 2004; Pal and Bhadada, 2020). Roszer and Ricote has summarized and reported the association of PPAR γ and hepatic ACE2 expression with the drug pioglitazone, but a sufficient inference of ACE2 expression in COVID-19 comorbidities was not established (Roszer and Ricote, 2010). Administration of pioglitazone along with ARBs and/or ACEi can be performed in a SARS-CoV-2 based case-control study to determine the plausible pathways linked with ACE2 overexpression. In hypertension and diabetes, ventricular remodeling and dysregulated pathways are attenuated by Ang-(1–7) (Marques et al., 2011; Zhang et al., 2014). Yun Zhang et al. reported improved cardioprotection with perindopril treatment decreasing the formation of Ang II and also inhibiting the generation of angiotensin (1–5) from angiotensin (1–7) (Hao et al., 2015). Thus, perindopril along with the ACE2 activity was found to be associated with decreased formation of angiotensin II followed by ADAM17 down-regulation (Patel et al., 2014; Chappel, 2019). Moreover, treatment with perindopril remarkably improved angiotensin (1–7) levels in plasma. Solar MJ et al. have administered the Telmisartan (belongs to ARB) a drug used to prevent stroke, heart attack, and kidney problems in mice. This study shows the increased ACE2 transcript and protein levels in the kidney of Telmisartan treated mice (Soler et al., 2009). Irbesartan a drug used to treat hypertension was treated to C57BL/6 mice which also reported an increased aortic ACE2 mRNA as well as protein expression (Jin et al., 2012). Both studies establish the role of ACE2 in preventing hypertension. Also, Oudit G Y et al. reported the effect of irbesartan along with ang (1–7) on restoring cardioprotective effects in ACE2-null mice (Patel et al., 2012). Irbesartan blocks the angiotensin II type 1 receptor pathway thus reducing the vasoconstriction load and induces antihypertensive effects. Supplementation of ang (1–7) along

with irbesartan reduced superoxide formation and attenuated NADPH oxidase activity. Further, it decreased p47phox and gp91phox activity and inhibited p47phox phosphorylation, thus attenuating NADPH oxidase activation and superoxide formation (Bendall et al., 2002; Zhong et al., 2004; Bodiga et al., 2011). Both, ACEi and ARBs are clearly established to increase the ACE2 levels. Likewise, several other medications such as Spironolactone and Eplerenone (both belong to Aldosterone antagonists) have been reported with ACE2 overexpression in experimental models (Keidar et al., 2005). Atorvastatin and Fluvastatin (belongs to Statin) were routinely used to reduce cholesterol can also upregulate renal and cardiac ACE2 expression (Tikoo et al., 2015; Shin et al., 2017). Notably, GLP agonists (liraglutide), DPP 4 inhibitors (Linagliptin), and NSAIDs (Ibuprofen) were reported to elevate ACE2 expression predominantly in the heart and lungs (Romani-Perez et al., 2015; Zhang et al., 2015; Qiao et al., 2015; Fandino et al., 2018). An alternative to ACEi and ARBs, all-trans retinoic acid (atRA) has notably ameliorated ACE2 articulation in the heart attributing towards the decrease of vasoconstriction in spontaneously hypertensive rats (SHR) suggesting that atRA might act as a therapeutic agent to prevent human essential hypertension (Beswick et al., 2001). Based on research and statistical investigations of COVID-19 infected people, several studies have mentioned important concerns over reconsidering the safety and leftover of ACEi and ARB's therapeutics in treating patients with hyper blood pressure and cardiovascular comorbidities. Though the association of ACEi and ARBs with the ACE2 upregulation in COVID-19 infected comorbidities is evident, researchers have suggested their concern on switching towards an alternative pharmacological agent for therapeutic intervention.

5. Regulatory pathways related to ACE2 expression

An official report proclaimed by the Italian National Institute of Health depicts that the most prevalent comorbidities among COVID patients were associated with arterial hypertension, diabetes mellitus, and ischemic cardiopathy (Onder et al., 2020). Further investigations confirm that 30% of patients exhibiting severe complications were taking ACEi drugs and 14% are taking ARB therapeutics. Recently, few clinical experts have revealed ACE2 overexpression among COVID-19 patient groups having hypertension, cardiovascular and diabetic comorbidities. ACE2 overexpression has also been noticed in patients taking ACEi/ARBs for their treatment. But the mild differences in expression are mainly depending upon the age and sex followed by monotherapy or combined therapy with ACEi and ARBs. ACE2 regulates the MasR signaling axis beside the ACE/Angiotensin II/AT1R regulation. The pathways associated with ACE2 regulation have shown that Ang II downregulates ACE2 (mRNA) transcripts in myocytes rather than fibroblasts. Tallant EA et al. reported the function of endothelin-1 in decreasing the ACE2 expression. The use of mitogen-activated protein kinase 1 (MAPK1) inhibitors with extracellular signal-regulated kinase 1/2 (ERK1/2) has also identified the role of endothelin-1 and Ang II in attenuating the ACE2 expression (Gallagher et al., 2008). In the case of mild to moderate inflammatory responses, non-steroidal anti-inflammatory drugs (NSAIDs) give relief for a period. However, long-term intake also increases the susceptibility to viral infections. Ibuprofen inhibits the prostaglandin synthesis from the arachidonic acid by non-selectively inhibiting the enzymatic activity of cyclooxygenase (COX) 1 and 2 (Bushra and Aslam, 2010). It mediates an increased sodium and water reabsorption due to the inhibition of prostaglandin synthesis, particularly Prostaglandin E2 (PGE2) and Prostaglandin I2 (PGI2) (Ricciotti and FitzGerald, 2011). Specifically, altered regulation in the ion and water leads to reduced renal perfusion followed by an upregulated ACE2 expression to facilitate a reverse action to reduce the perfusion (Turner, 2015; Mizuiru and Ohashi, 2015). Further, angiotensin II was reported to reduce the ACE2 activity while ADAM17 (referred to as TNF α -converting enzyme) upregulation in murine models. The signaling pathway was attenuated by blocking the Ang

II/AT1R axis (Patel et al., 2014). Thus, receptor blockade exhibits a vital role in downregulating the kinase pathway of 1/2 and ADAM17 activity which prevents the shedding of ACE2. ADAM17 also regulates the shedding of extracellular domains and the activation of TNF- α , thereby promoting autocrine and paracrine activity. Therefore, TNF- α activation of tumor necrosis factor receptor (TNFRs) not only increases the ADAM17 activity but also increases the shedding of ACE2 in the RAS-based feedback loop (Gheblawi et al., 2020). Few reports have highlighted the role of the ACE2 signaling in regulating the activity of TNF- α and transforming growth factor- β (TGF- β) (cytokines) in the cases of cardiovascular condition and pulmonary hypertension (Grobo et al., 2007; Zeng et al., 2009; Purushothaman et al., 2013). Reduced expression of TGF- β , Smad, and membrane linked glycoprotein CD44 with telmisartan treatment demonstrated the pathways associated with negative control of ACE2 expression (Sriramula et al., 2011). Impact of ACE2 upregulation on the pro-inflammatory cytokines in the signaling cascade has not been analyzed in detail. However, the counter-regulatory role of sirtuin 1 in association with interleukin-1 has suggested an interlinked, yet investigatory pathway for ACE2 expression. In obese condition, the adipose tissue is subjected to hyperplasia and hypertrophy followed by endoplasmic stress. Irregular, vascularization results in hypoxia, necrosis, excess secretion of inflammatory adipokines, cytokines, and chemokines (Choe et al., 2016; Grant and Stephens, 2015). Based on adipocyte dysfunction, altered immunoregulation leads to the secretion of specific cytokines as well as TNF- α , interferon-gamma (IFN- γ) and interleukin-6 (IL-6) (Exley et al., 2014). In cases of obese adipocyte tissues, the excess secretion of pro-inflammatory cytokines are regulated by NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome. Several studies have reported the role of NLRP3 in immune regulation, lipid metabolism, and adipocyte function (Vandanmagsar et al., 2011). Further, ACE2 has been reported to be overexpressed in the pathophysiological condition of diabetes and obese adipocyte tissues. Excess accumulation of fatty acid not only influences the metabolic signaling but also facilitates the activation of crucial proteins like peroxisome proliferator-activated receptor gamma (PPAR γ) (Kliwer et al., 1997). Thus, diabetes and obese patients are susceptible to the viral infection not only on the basis of ACEi and ARB medications but also irregular physiological conditions that facilitate irregular immunoregulation as well as deregulated metabolism. Further, the dysregulated pathophysiological condition results in the overexpression of ACE2 under cell energy stress. In a study, it was found that 5-amino-4-imidazole carboxamide riboside (AICAR) activated the AMPK pathway (Bai et al., 2016). AMP-activated protein kinase (AMPK) acts as an inhibitory switch to balance the energy-consuming pathways (Hardie et al., 2012). AMPK activates transcriptional mediators like sirtuin 1 and histone deacetylase that regulates metabolic pathways through multiple transcription factors (Tomas et al., 2002). Brookes Paul S et al. reported ACE2 overexpression after treating the ACE2 promoter with IL-1 β in a time gap of 48hrs, thus the expression of ACE2 transcript (mRNA) was shown as highly time-dependent (Nadtochiy et al., 2011). Besides, in experimental hypertension conditions, rho-kinase inhibition by fasudil (inhibitor) has improved vasodilatation and ACE2 activity. Moreover, fasudil upregulated angiotensin (1–9) levels without any modifications in angiotensin (1–7) plasma levels (Clarke et al., 2014). Thus, the Rho-kinase pathway regulates the anti-hypertensive signaling cascade and improves cardioprotective effects (Ocaranza et al., 2011). Zhang and their group assessed the clinical significance of valsartan and enhancer-binding protein β (C/EBP β) on the treatment of type I diabetes and ACE2 expression. The enhancer-binding protein β is a specific sequence CCAAT associated transcription factor which up-regulates of ACE2 expression by its overexpression. The transcription factor C/EBP β also increased angiotensin (1–7) levels, but a less significant difference was determined (Tie et al., 2017).

6. Data-mining on genes and pathways associated with ACE2 regulation

Text mining was performed with comorbidities i. e arterial hypertension, smoking, lung fibrosis, and bronchial asthma. This study has identified the association of histone modifiers with the ACE2 expression. The genes associated with the upregulation of ACE2 were assessed by pathway enrichment analysis. KDM5B was one of the genes linked with the ACE2 regulation. Histone modifications (acetylation/methylation) at H3K27/H3K4 were also associated with ACE2 regulation (Pinto et al., 2020). Moreover, research data highlighted the association of genes related to insulin secretion and interleukin-6 overexpression with SARS-CoV-2 comorbidities. Further, the insulin gene also regulates the Sirtuin 1 activity (Liang et al., 2009). Also, the upregulation of Sirtuin 1 was observed in the lungs of SARS-CoV-2 infected cases. It has also been demonstrated that Sirtuin 1 can epigenetically regulate ACE2 under an alarming situation of stress. Clinical studies have shown that histone deacetylase inhibitors may inhibit the expression of ACE2 (Dell’Oma et al., 2019). Based on data interpretation, genes that were positively correlated with ACE2 expression can facilitate epigenetic modification i. e histone (acetylation/deacetylation), gene activation, and chromatin dynamics. Mokuda S et al. revealed the association of IL-6 and Signal transducer and activator of transcription 3 (STAT3) signaling with ACE2 expression in rheumatoid synovium (Mokuda et al., 2020). Lee and Hennighausen has studied the link between interferon- α/β and γ along with STAT components in Janus kinase (JAK)/STAT signaling with reference to ACE2 activity in Type II Pneumocytes (Fig. 2) (Hennighausen and Lee, 2020). A recent report shows that Histone deacetylase inhibitor (HDACi) suppresses both ACE2 and ABO simultaneously (Takahashi et al., 2020). The interconnected pathways linked with ACE2 expression have been studied against pathological conditions, but a significant concern towards SARS-CoV-2 infection is still under investigation. Further, clinical approaches must be broadened for analyzing the parallel effect of inhibitors and inflammatory responses which in turn can auto-regulate significant cofactors concerning ACE2 overexpression. Several reports have speculated the increased expression of ACE2 due to ACEi/ARB therapeutic administration, but adequate evidence is still needed. Thus, the molecular paradigm of SARS-CoV-2 pathogenesis in association with ACE2 expression requires an integrative and elaborative analysis for complete understanding and effective treatment of the viral outbreak.

7. Conclusion

Attachment of SARS-CoV-2 with the ACE2 attenuates the receptor function, thus facilitating virus internalization. The counter-regulation of ng II regulated AT1 receptor signaling in pulmonary vasoconstriction and inflammatory damage is balanced by ACE2 activity to prevent cell damage. Research groups have analyzed alleviating ACE2 expression in SARS-CoV-2 infected patients who are dependent on ARBs and/or ACE inhibitors. In the case of diabetes mellitus, few in vivo studies have reported an association between ACEi/ARBs, and anti-diabetic medications on ACE2 upregulation, but significant clinical investigations are still required. ACEi and ARB linked ACE2 upregulation in hypertension and cardiovascular comorbidities also require significant evaluation. Imperative study on specific inflammatory molecules associated with positive regulation of ACE2 expression might provide the plausible pathways linked with SARS-CoV-2 pathophysiology. We have tried to address the significant molecular pathways associated with ACE2 expression which can be further clinically investigated to understand the elevated chance of developing SARS-CoV-2 in patients subjected to higher levels of ACE2. Currently, no guidelines have been provided by the health administrations and government agencies on shifting from ACEi and ARBs towards other alternative medications because of lack of evidence. Thus, patients with hypertension, diabetes mellitus, and cardiovascular problems should continue with ACEi and

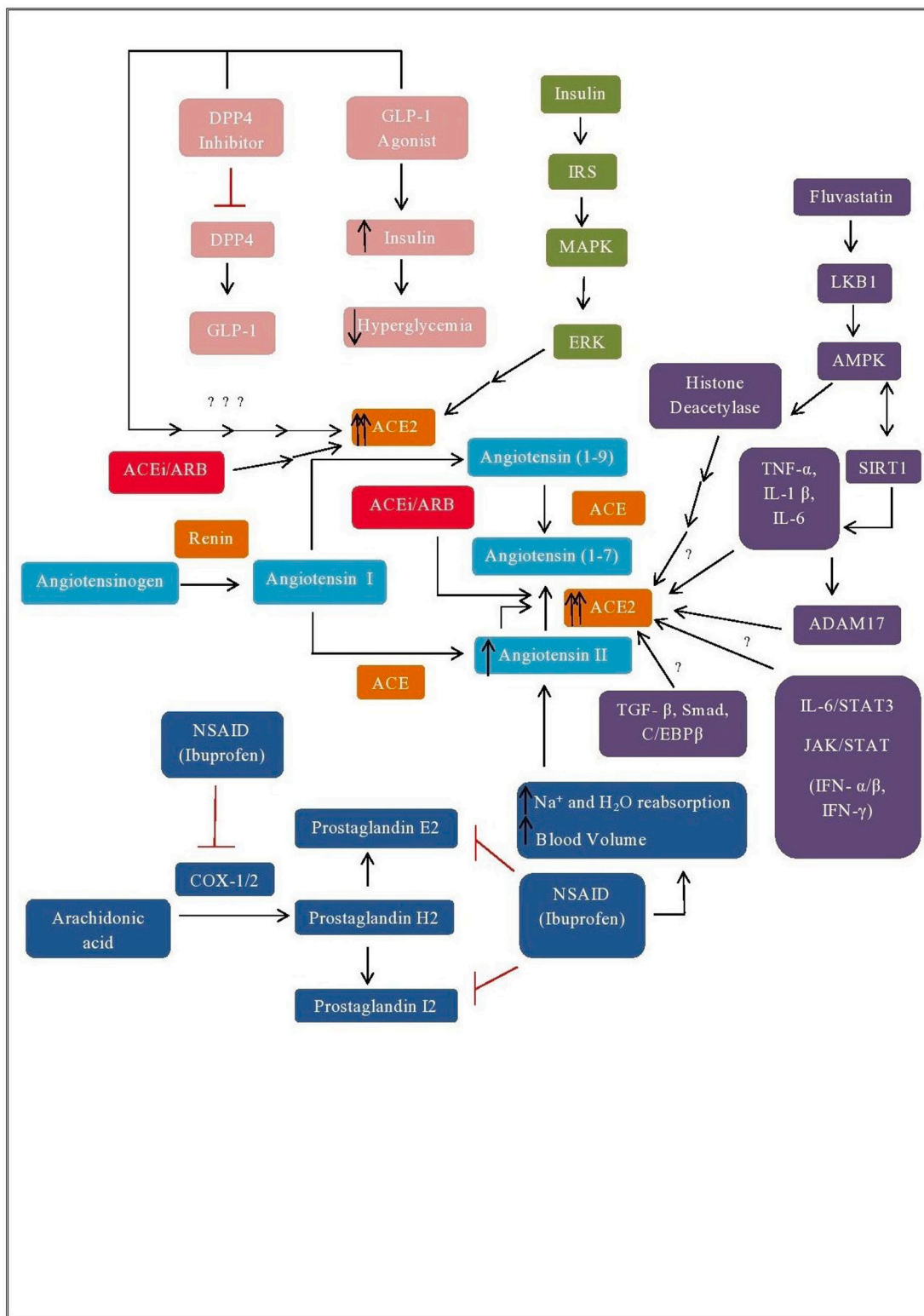


Fig. 2. Schematic representation of RAAS associated AT1 and AT2/Mas receptor activity. ACEi inhibits the function of ACE I and ARBs inhibit the downstream signaling of AT1 receptor. AMPK/SIRT1 induces ACE2 regulation. Cytokines and Interferon's upregulating ACE2 expression through JAK/STAT signaling. IL-6 mediated STAT3 signaling upregulates ACE2. In comparison with the ACEi and ARBs, insulin, Non-steroidal anti-inflammatory drugs, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide 1 receptor agonists in association with crucial molecular pathways regulate the ACE2 expression.

ARBs with caution. Further, investigations and distinctive molecular analyses are required to understand the molecular paradigm of ACE2 expression in association with SARS-CoV-2 pathogenesis.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejphar.2021.173899>.

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Author contributions

SRIDHAR Jayavel: Conceptualization, Supervision, Reviewing-editing.

RAHUL Parit: Investigation, Data curation, Original draft preparation.

All authors read and approved the final manuscript.

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