Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Renin-angiotensin-system, a potential pharmacological candidate, in acute respiratory distress syndrome during mechanical ventilation

Di Wang, Xiao-qing Chai, Costan G. Magnussen, Graeme R. Zosky, Shu-hua Shu, Xin Wei, Shan-shan Hu

Department of Anesthesiology and Pain Medicine, Anhui Provincial Hospital, First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China (USTC), Hefei, 230001, Anhui, China

Menzies Institute for Medical Research, College of Health and Medicine, University of Tasmania, Hobart, 7001, Tasmania, Australia

Research Centre of Applied and Preventive Cardiovascular Research, University of Turku, Turku, 20520, Finland

School of Medicine, College of Health and Medicine, University of Tasmania, Hobart, 7001, Tasmania, Australia

Institute of Clinical Pharmacology, Anhui Medical University, Hefei, 230032, Anhui, China

ARTICLE INFO

Keywords:
Renin-angiotensin system (RAS)
Acute respiratory distress syndrome (ARDS)
Mechanical ventilation
Ventilator-induced lung injury (VILI)

ABSTRACT

While effective treatments for acute respiratory distress syndrome (ARDS) are lacking, mechanical lung ventilation can sustain adequate gas exchange in critically ill patients with respiratory failure due to ARDS. However, as a result of the phenomenon of ventilator-induced lung injury (VILI), there is an increasing need to seek beneficial pharmacological therapies for ARDS. Recent studies have suggested the renin-angiotensin system (RAS), which consists of the ACE/Ang-II/AT1R axis and ACE2/Ang-(1–7)/MasR axis, plays a dual role in the pathogenesis of ARDS and VILI. This review highlights the deleterious action of ACE/Ang-II/AT1R axis and the beneficial role of ACE2/Ang-(1–7)/MasR axis, as well as AT2R, in VILI and ARDS, and also discusses the possibility of targeting RAS components with pharmacological interventions to improve outcomes in ARDS.

1. Introduction

Acute respiratory distress syndrome (ARDS) is a devastating disorder characterized by overwhelming pulmonary inflammation leading to hypoxemia and respiratory failure [1]. ARDS severity can be categorized as mild (200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg), moderate (100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg), or severe (PaO2/FIO2 ≤ 100 mm Hg) [1]. Approximately 10% of patients admitted to intensive care units (ICUs) are diagnosed with ARDS according to the Berlin Definition, representing nearly 3 million patients with ARDS globally per annum [1–4]. Different from the classification in Berlin definition, recent studies have suggested that ARDS can be stratified into two biological phenotypes, ‘hypo-inflammatory’ and ‘hyper-inflammatory’ (also referred to as ‘reactive’). The hyper-inflammatory phenotype has more severe clinical features but responds to a range of treatments including PEEP, fluid management and pharmacotherapy [5–7]. Despite significant insights into the pathophysiology, once ARDS is established, patient mortality is high (up to 45%), and evidence-based therapeutic options are limited [1–4]. Mechanical ventilation, which supports adequate gas exchange, is a life-saving intervention for critically ill patients with respiratory failure. Unfortunately, mechanical ventilation can also contribute to lung injury via a process known as ventilator-induced lung injury (VILI), also termed as ventilator-associated lung injury (VALI), with a prevalence of 6.2% among mechanically ventilated patients [8]. Historically, the application of potentially injurious mechanical ventilation using large tidal volumes (Vt) and high peak airway pressure (Ppeak) increased the risk of development of ARDS both the ICU (odds ratio 2.6 for Vt > 700 mL and 1.6 for Ppeak > 30 cm H2O) and during surgical ventilation (odds ratio 1.56 for each mL/kg increase of intraoperative Vt) [8,9].

VILI is characterized by inflammatory cell infiltration in the lungs, loss of the epithelial and endothelial integrity, increased capillary permeability, deposition of extracellular matrix and interstitial pulmonary edema and fibrosis [10,11]. To improve the clinical relevance, a two-hit model, with the LPS challenge (intratracheal or intraperitoneal) followed by injurious ventilation, has been applied in preclinical studies to mimic pre-existing sepsis which is the most common cause of ARDS [12,13]. VILI, which can occur in previously normal lungs or worsens pre-existing ARDS, can occur via a range of mechanisms (1) including tissue stress caused by over-distension of lung alveoli exposed to increasing transpulmonary pressures (baro-volutrauma), (2) and repeated alveoli recruitment and de-recruitment.
causing high local shearing forces (atelectrauma), (3) these mechanical responses trigger recruitment of leukocytes and the release of chemokines/cytokines leading to pulmonary and systemic inflammatory response (biotrauma) [10,11]. Accordingly, various artificial ventilation strategies, such as a small VT to avoid lung alveoli over-distension as a response (biotrauma) [10,11].

Recently, several studies have suggested a role for the renin-angiotensin system (RAS) in ARDS and VILI [12,16–18]. While the RAS is well known to have a primary role in the control of salt retention and blood pressure, its role in inflammation and injury suggest that it may be a novel therapeutic option for the treatment of ARDS and VILI. The present review highlights the role of angiotensin-II (Ang-II), and other RAS components, in the inflammation and injury associated with VILI.

2. Distribution of pulmonary RAS components

Renin, released from the juxtaglomerular cells of the kidney, cleaves the macroglobulin precursor angiotensinogen into inactive decapetide angiotensin-I (Ang-I). Ang-I enters circulation and is further transformed to the active octapeptide Ang-II through enzymatic cleavage by angiotensin converting enzyme (ACE) which is distributed both systematically and locally [19,20]. Ang-II acts as a prominent mediator in the RAS by binding to angiotensin type 1 receptor (AT1R) or type 2 receptor (AT2R) [19,20]. Furthermore, Ang-II is cleaved by angiotensin converting enzyme 2 (ACE2) forming angiotensin-(1–7) (Ang-(1–7)), which binds with Mas receptor (MasR) to antagonize AT1R-mediated effects, in most cases [21,22]. There has been considerable interest in the balance between ACE/Ang-II/AT1R axis and the ACE2/Ang-(1–7)/MasR axis, where recent evidence suggests that Ang-(1–7) may activate AT2R to antagonize AT1R-mediated effects [23,24].

In addition to the systemic RAS, there is local expression of almost all RAS components in the lung, which is a major source of ACE and, therefore, a major site of systemic Ang II synthesis. Metzger and colleagues found that ACE is expressed abundantly in capillary endothelial cells in the entire capillary network of the alveoli in human lungs [25,26]. As a result, pulmonary vasoconstriction occurs readily in response to hypoxia which is essential for ventilation-perfusion matching. In contrast, Wiener and colleagues found that ACE2 is primarily located in Clara cells and type II alveolar epithelial cells in murine lungs [27]. Pulmonary ACE2 appears to have a role in regulating Ang II/Ang-(1–7) levels. Recently, studies have shown that local RAS components are distributed in lung-resident immune and inflammatory cells. Thus, there is the potential for the RAS system to have a range of effects in the context of lung injury related to VILI and ARDS.

3. ACE/Ang-II/AT1R axis

3.1. Activation of ACE/Ang-II/AT1R axis in VILI and ARDS

ACE/Ang-II expression is markedly increased in patients with ARDS and patients with sepsis, the most common cause of ARDS [28,29]. Clinical epidemiological studies have shown a significant association between polymorphisms in the Ace gene and the susceptibility to ARDS [30–33]. For example, Marshall and colleagues found that the Ace I/D genotype frequency, but not Ace I/I polymorphism, was increased among patients with ARDS compared with controls, with those homozygous for the D allele conferring higher levels of ACE and Ang-II in tissue and serum [30]. Up-regulation of ACE activity has been broadly associated with a range of ARDS related conditions including pneumonia, aspiration, trauma, and pancreatitis [34–36]. Notably, during mechanical ventilation, Weston-van Asperen and colleagues showed that mechanical ventilation up-regulates ACE activity, resulting in increased conversion of Ang-I to Ang-II [13,17,18]. In addition, respiratory insults can cause a marked increase in AT1R expression [17,18,34,35], with potential downstream effects on activation of ACE/Ang-II signaling. For example, Jeng and colleagues found that AT1R expression, measured at the RNA and protein level, increased with activation of ACE/Ang-II following injurious ventilation in an experimental model of VILI, and further mediated the downstream nuclear translocation of cytosolic fraction of NF-κB [17] which is strongly linked to inflammation.

3.2. Downstream effects of the ACE/Ang-II/AT1R axis in VILI and ARDS

A number of studies have shown that Ang-II is a critical mediator of the inflammatory cascade and alveolar epithelial injury associated with ARDS. For example, Ang-II induces dose-dependent apoptosis in human and rat alveolar epithelial cells (AECs) through its interaction with AT1R [37–40]. A number of different signaling pathways are involved in the induction of apoptosis in AECs by Ang-II/AT1R [41,42]. Wang and colleagues found that activation of pro-oxidant signals and superoxide production by Ang-II/AT1R pathway contributed to hypoxia-induced lung injury and fibrosis [41]. Li and colleagues found that Ang-II/AT1R pathway caused activation of NF-κB and JAK2/STATs pathways, and induced apoptosis in AECs in response to seawater inhalation-induced lung injury [42]. Similarly, high Ang-II/AT1R levels may also activate the secretion of pro-inflammatory cytokines, promote macrophages and neutrophils chemotaxis and contribute to VILI [43–45]. For instance, Jiang and colleagues found that Ang-II levels in the lung correlated positively with TNF-α and macrophage inflammatory protein-2 (MIP-2) levels in bronchoalveolar lavage fluid (BALF) in a rodent model of VILI [39]. Critically, TNF-α is necessary for the induction of apoptosis in AECs by the ACE/Ang-II/AT1R axis [46]. This response is likely to be driven by activation of the NF-κB pathway whereby NF-κB activation in sepsis-induced ARDS, associated with an increase of Ang-II, leads to phosphorylation of p38MAPK leading to the production of pro-inflammatory cytokines [47].

3.3. Pharmacological modulation of the ACE/Ang II/AT1R axis for the treatment of VILI and ARDS

The deleterious role of ACE/Ang-II/AT1R axis activation is supported by the protective effect of ACE inhibitors in experimental studies. Several independent research groups have shown that ACE inhibitors and angiotensin receptor blockers (ARBs) can attenuate the lung edema, lung AECs apoptosis, and microvascular permeability caused by ARDS [13,43,44,48]. For example, Liu and colleagues found that losartan, an ARB, attenuated neutrophilia in LPS-induced respiratory inflammation in mice which was associated with inhibition of dendritic cell maturation and suppression of Th1 and Th17 immune responses [49]. In line with this, another study found that losartan attenuated lung injury induced AECs apoptosis and ROS generation [42]. These observations are likely to be due to inhibition of NF-κB activation and p38MAPK phosphorylation [47]. Similar observations have been reported in models of VILI in response to ACE inhibitors, such as captopril [13,17]. However, while experimental models using ARBs and ACE inhibitors have been promising, strong evidence from clinical studies about the association between the use of ARBs and ACE inhibitors and outcome of ARDS and VILI are still lacking, especially high quality RCTs (see Table 1).
3.4. Emerging protective role of AT2R in ARDS and VILI

AT2R is normally only expressed at low levels by lung epithelial cells, endothelial cells, fibroblasts, and activated myofibroblasts in healthy adults [50]. However, pulmonary AT2R, as well as AT1R, are abundantly up-regulated in chronic lung disease such as chronic obstructive pulmonary disease (COPD) as well as idiopathic pulmonary fibrosis (IPF) [50,51]. For example, as shown in the study by Jerng and colleagues, lung tissue AT2R mRNA, as well as Ang-II and AT1R mRNA levels, were markedly increased in the high-volume ventilation in rats [17]. While AT2R often has a similar increase in ARDS and VILI as AT1R, AT1R opposes AT2R by promoting injury and fibrosis. In line with this, a study by Imai and colleagues showed that Ang II knock-out mice had more severe pathology in response to acid aspiration induced lung injury than wild-type controls [34]. A number of beneficial actions of AT2R in lung injury have recently been demonstrated [52-54]. Bruce and colleagues found that treatment with C21, an AT2R non-peptide agonist, ameliorates pulmonary fibrosis and prevents right ventricular fibrosis in pulmonary hypertension, and these beneficial effects are abolished by co-administration of the AT2R antagonist, PD123319 [52]. Furthermore, Rathinasabapathy and colleagues found that stimulation of the AT2R by C21 attenuates bleomycin-induced lung injury by alleviating lung inflammation and fibrosis [53]. A double-blind and placebo-controlled Phase IIa study has been approved by the European Union Clinical Trials Register with EudraCT Number: 2017-004923-63 and begun to evaluate the effect of C21 on fibrotic lung injury and the safety of C21.

4. ACE2/Ang-(1–7)/MasR axis

4.1. Inhibition of ACE2/Ang-(1–7)/MasR axis in VILI and ARDS

ACE2, a homologue of ACE, cleaves a single residue from Ang-II to generate Ang-(1–7) [55,56]. Thus, ACE2 acts as a negative regulator of RAS by inactivating Ang-II. While originally identified as a potential receptor for SARS corona virus [57], lung expression of ACE2 has also been shown to be suppressed in ARDS [58,59]. For example, the acid aspiration-induced lung injury is associated with markedly reduced ACE2 protein expression and elevated Ang-II levels [34]. Decreases of ACE2 activity, and concomitant enhancement of ACE activity occur in response to LPS-induced lung injury [45]. The importance of ACE2 in ARDS has been confirmed in knock-out mouse models whereby inhibition of Ace2 expression resulted in enhanced vascular permeability, increased lung edema, severe inflammatory cell infiltration and impaired lung function [34,60]. Supplementation with recombinant ACE2 was able to improve these outcome measures [34,60], confirming that
4.2. Downstream effects of the ACE2/Ang-(1–7)/MasR axis in VILI and ARDS

While ACE2 partially blocks Ang-II/AT1R signaling, the beneficial role of this mediator in ARDS is primarily attributed to activation of the Ang-(1–7)/MasR signaling pathway [59]. This has been confirmed in a number of studies where supplementation with Ang-(1–7) alleviated lung edema, myeloperoxidase activity, lung injury, and pulmonary vascular resistance in mouse models of ARDS [59,61]. Furthermore, Chen and colleagues found that treatment with Ang-(1–7) attenuated the lung fibrosis and collagen deposition in the LPS-induced lung injury through suppression of TGF-β signaling [62]. Blockade of MasR, largely prevents the protective effects of Ang-(1–7) demonstrating the importance of downstream activation of this pathway in models of ARDS [59,61]. The mechanisms of the beneficial effects on outcomes in these models include inhibition of apoptosis in AECs and pulmonary microvascular endothelial cells (PMVECs), as well as a reduction in the proliferation and migration of lung fibroblasts. For instance, studies by Ang-(1–7)/MasR enhances survival of AECs, which normally show excessive apoptosis in ARDS [63,64]. Gopallawa and colleagues found that Ang-(1–7)/MasR enhanced mitogen-activated protein kinase phosphatase-2 (MKP-2) which drives apoptosis of AECs [65]. A similar effect has been shown in PMVECs whereby activation of the ACE2/Ang-(1–7)/MasR axis reduced apoptosis and cytokine secretion in PMVECs by inhibiting the phosphorylation of JNK/NF-kB which could be restored by MasR blockade [66].

4.3. Pharmacological modulation of the ACE2/Ang-(1–7)/MasR axis for the treatment of VILI and ARDS

Pharmacological manipulation of ACE2/Ang-(1–7)/MasR axis, at each level, has been shown to exert a protective effect in various experimental models of ARDS (see Table 1). Specifically, supplementation with recombinant human angiotensin-converting enzyme 2 (rhACE2), angiotensin-(1–7) (Ang-(1–7)), Mas receptor (MasR), alveolar epithelial cells (AECs), pulmonary microvascular endothelial cells (PMVECs), lipopolysaccharide (LPS).

**Table 1**

| Agent | Model | Outcome |
|-------|-------|---------|
| ACE/Ang-II/AT1R axis | Captopril | A two-hit ARDS model with LPS pretreatment followed by mechanical ventilation | Captopril decreased lung injury scores and improved lung function. Captopril attenuated inflammatory response to a less extent than by Losartan [13] |
|        | Losartan | A two-hit ARDS model with LPS pretreatment followed by mechanical ventilation | Losartan reduced ACE activity and Ang II level, whereas enhanced ACE2 activity and Ang (1–7) level [12]. Losartan decreased high ACE activity and Ang II level and inhibited AT1R expression [13] |
|        | Losartan | LPS induced-ARDS model | Losartan improved ACE2 activity [45], suppressed NF-kappaB activation, and inhibited phosphorylation of p38MAPK [47], reduced elevation of Ang II/AT1R, suppressed AECs apoptosis [40] |
|        | Captopril | Ventilator-induced lung injury model | Captopril attenuated lung injury score, protein leakage, myeloperoxidase activity, pro-inflammatory cytokine levels and NF-kappaB activity [17,39] |
|        | Losartan | Ventilator-induced lung injury model | Losartan prevented inflammation, lung AECs apoptosis, and microvascular permeability, reduced elevation of Ang II/AT1R [43,44] |
| AT2R | C21 Pulmonary hypertenion model | C21 reversed pulmonary fibrosis and prevented right ventricular fibrosis. C21 improved right heart function, reduced pro-inflammatory cytokines [52] |
|        | C21 Bleomycin-induced lung fibrotic injury | C21 reduced infiltration of macrophages and diminished pulmonary collagen accumulation and normalized cardiac function [53] |
|        | C21 Lung injury model induced by repeated pulmonary lavage | C21 diminished TNF-alpha and IL-6, but did not improve pulmonary gas exchange or lung edema [54] |
| ACE2/Ang-(1–7)/MasR axis | Ang-(1–7) | A two-hit ARDS model with LPS pretreatment followed by mechanical ventilation | Ang-(1–7) decreased lung injury scores and improved lung function and oxygenation [12] |
|        | Ang-(1–7) Ventilator- or acid aspiration-induced lung injury | Alleriation of lung edema, inflammation and fibrosis, improvement of survival of PMVECs, inhibition of proliferation of lung fibroblasts [61] |
|        | LPS induced-ARDS model | Ang-(1–7) reduced lung fibrosis and collagen accumulation, and transforming growth factor-β and Smad2/3 [62] |
|        | rhACE2 Bleomycin-induced lung injury | rhACE2 improved survival, and lung function and decreased lung inflammation and fibrosis [69] |
|        | LPS induced-ARDS model | rhACE2 reversed the ACE2/AEC imbalance and increased Ang-(1–7) levels, thus reducing LPS-induced apoptosis and inflammation of PMVECs [66] |
|        | rhACE2 A placebo-controlled phase II trial in patients with ARDS | rhACE2 led to a decrease of Ang-II and IL-6 although the study was not powered to detect significant changes in clinical outcomes [66] |

Abbreviations: angiotensin converting enzyme (ACE), angiotensin-II (Ang-II), angiotensin type 1 receptor (AT1R), angiotensin type 2 receptor (AT2R), compound 21 (C21), angiotensin converting enzyme 2 (ACE2), recombinant human angiotensin converting enzyme 2 (rhACE2), angiotensin-(1–7) (Ang-(1–7)), Mas receptor (MasR), alveolar epithelial cells (AECs), pulmonary microvascular endothelial cells (PMVECs), lipopolysaccharide (LPS).

ACE2 plays a beneficial role in lung injury and, potentially, ARDS.
that many pharmacological candidates against ARDS have been shown less effective despite identification of potentially promising candidates in preclinical studies. In particular, multiple RAS components have been experimentally assessed, but only two targets and the related compound (rhACE2 and C21) have shown promise and have progressed to further evaluation of clinical trial. For this discrepancy of results between clinical trial and preclinical research, a frequently mentioned reason is heterogeneity of ARDS. Some studies had clearly shown heterogeneity of ARDS and the variability of ACE activity have a potential effect on the outcome of ARDS patients. Importantly, since ARDS is a sort of highly-heterogeneous disease, subgroup analysis based on two biological phenotypes, which indicate different responses to treatment, was increasingly considered to be highly applicable for evaluation of treatment responsiveness. Similarly, Ace I/D genotype offers a possibility to predict the risk of ARDS occurrence. Thus, consideration with an emphasis on biological phenotypes of ARDS and Ace I/D genotype open perspectives to precision medicine with target therapy for ARDS. While some experimental, and a limited number of clinical trials have shown that the RAS is a promising therapeutic target, large scale, well-designed clinical trials, in parallel with mechanistic studies, are required to determine whether these treatments will benefit these critically ill patients. (see Table 1)

Declarations of interest

None.

Acknowledgement

This study was supported by grants from National Natural Science Foundation of China (No. 81503080), Anhui Provincial Key Research and Development Project Foundation (No.1804h08020286).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pupt.2019.101833.

References

[1] A.D.T. Force, et al., Acute respiratory distress syndrome: the Berlin Definition, J. Am. Med. Assoc. 307 (23) (2012) 2526–2533.
[2] G. Bellani, et al., Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries, J. Am. Med. Assoc. 315 (8) (2016) 784–800.
[3] B.A. McNicholas, G.M. Rooney, J.G. Laffey, Lessons to learn from epidemiologic studies in ARDS, Curr. Opin. Crit. Care 24 (1) (2018) 41–48.
[4] E. Fan, D. Brude, A.S. Slutsky, Acute respiratory distress syndrome: advances in diagnosis and treatment, J. Am. Med. Assoc. 319 (7) (2018) 698–710.
[5] C.S. Calfee, et al., Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials, Lancet Respir. Med. 2 (8) (2014) 611–620.
[6] C.S. Calfee, et al., Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial, Lancet Respir. Med. 6 (9) (2018) 691–698.
[7] K.R. Famou, et al., Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy, Am. J. Respir. Crit. Care Med. 195 (3) (2017) 331–338.
[8] O. Gajic, et al., Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients, Intensive Care Med. 31 (7) (2005) 922–926.
[9] E.R. Fernandez-Perez, et al., Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy, Anesthesiology 105 (1) (2006) 14–18.
[10] A.S. Slutsky, V.M. Ranieri, Ventilator-induced lung injury, N. Engl. J. Med. 369 (22) (2013) 2126–2136.
[11] M. Biehl, M.G. Kashioris, O. Gajic, Ventilator-induced lung injury: minimizing its impact in patients with or at risk for ARDS, Respir. Care 58 (6) (2013) 927–937.
[12] M.M. Westen-van Asperen, et al., Acute respiratory distress syndrome leads to further evaluation of clinical trial. For this discrepancy of results between clinical trial and preclinical research, a frequently mentioned reason is heterogeneity of ARDS. Some studies had clearly shown heterogeneity of ARDS and the variability of ACE activity have a potential effect on the outcome of ARDS patients. Importantly, since ARDS is a sort of highly-heterogeneous disease, subgroup analysis based on two biological phenotypes, which indicate different responses to treatment, was increasingly considered to be highly applicable for evaluation of treatment responsiveness. Similarly, Ace I/D genotype offers a possibility to predict the risk of ARDS occurrence. Thus, consideration with an emphasis on biological phenotypes of ARDS and Ace I/D genotype open perspectives to precision medicine with target therapy for ARDS. While some experimental, and a limited number of clinical trials have shown that the RAS is a promising therapeutic target, large scale, well-designed clinical trials, in parallel with mechanistic studies, are required to determine whether these treatments will benefit these critically ill patients. (see Table 1).
R. Wang, et al., Apoptosis of lung epithelial cells in response to TNF-alpha requires angiotensin II generation de novo, J. Cell. Physiol. 185 (2) (2000) 253–259.

L. Shen, et al., Losartan prevents sepsis-induced acute lung injury and decreases activation of nuclear factor kappα and mitogen-activated protein kinases, Shock 31 (5) (2009) 500–506.

S. Amsen, et al., The Angiotensin-converting enzyme inhibitor captopril inhibits poly(ADP-ribose) polymerase activation and exerts beneficial effects in an ovine model of burn and smoke injury, Shock 36 (4) (2011) 402–409.

L. Liu, et al., Losartan, an antagonist of AT1 receptor for angiotensin II, attenuates lipopolysaccharide-induced acute lung injury in rat, Arch. Biochem. Biophys. 481 (1) (2009) 131–136.

G.R. Bullock, et al., Distribution of type-1 and type-2 angiotensin receptors in the normal human lung and in lungs from patients with chronic obstructive pulmonary disease, Histochem. Cell Biol. 115 (2) (2001) 117–124.

M. Königshoff, et al., The angiotensin II receptor 2 is expressed and mediates angiotensin II signaling in lung fibrosis, Am. J. Respir. Cell Mol. Biol. 57 (6) (2007) 649–656.

E. Bruce, et al., Selective activation of angiotensin AT2 receptors attenuates progression of pulmonary hypertension and inhibits cardiopulmonary fibrosis, Br. J. Pharmacol. 172 (9) (2015) 2219–2231.

A. Rathinasabapathy, et al., The selective angiotensin II type 2 receptor agonist, compound 21, attenuates the progression of lung fibrosis and pulmonary hypertension in an experimental model of bleomycin-induced lung injury, Front. Physiol. 9 (2018) 180.

M. Menk, et al., Angiotensin II type 2 receptor agonist Compound 21 attenuates pulmonary inflammation in a model of acute lung injury, J. Inflamm. Res. 11 (2018) 169–178.

S.R. Tripis, et al., A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase, J. Biol. Chem. 275 (43) (2000) 33238–33243.

G.C. Douglas, et al., The novel angiotensin-converting enzyme (ACE) homolog, ACE2, is selectively expressed by adult Leydig cells of the testis, Endocrinology 145 (10) (2004) 4703–4711.

K. Kuba, et al., A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury, Nat. Med. 11 (8) (2005) 875–879.

Y. Imai, K. Kuba, J.M. Penninger, The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice, Exp. Physiol. 93 (5) (2008) 543–548.

R.M. Westen-van Asperen, et al., Imbalance between pulmonary angiotensin-converting enzyme and angiotensin-converting enzyme 2 activity in acute respiratory distress syndrome, Pediatr. Crit. Care Med. 14 (9) (2013) e438–e441.

G.J. Rey-Purra, et al., Angiotensin converting enzyme 2 abrogates bleomycin-induced lung injury, J. Mol. Med. (Berl.) 90 (6) (2012) 637–647.

N. Klein, et al., Angiotensin-(1-7) protects from experimental acute lung injury, Crit. Care Med. 41 (11) (2013) e334–e343.

Q. Chen, et al., Angiotensin(1-7) attenuates lung fibrosis by way of Mas receptor in acute lung injury, J. Surg. Res. 185 (2) (2013) 740–747.

B.D. Uhal, et al., Regulation of alveolar epithelial cell survival by the ACE-2/angiotensin 1-7/Mas axis, Am. J. Physiol. Lung Cell Mol. Physiol. 301 (3) (2011) L269–L274.

M. Zhang, et al., ACE-2/ANG1-7 ameliorates ER stress-induced apoptosis in seawater aspiration-induced acute lung injury, Am. J. Physiol. Lung Cell Mol. Physiol. 315 (6) (2013) L1015–L1027.

I. Gopallawa, B.D. Uhal, Angiotensin-(1-7)/mas inhibits apoptosis in alveolar epithelial cells through upregulation of MAP kinase phosphatase-2, Am. J. Physiol. Lung Cell Mol. Physiol. 310 (3) (2016) L240–L248.

Y. Li, et al., Angiotensin-converting enzyme 2/angiotensin (1-7)/Mas axis prevents lipopolysaccharide-induced apoptosis of pulmonary microvascular endothelial cells by inhibiting JNK/NF-kappα pathways, Sci. Rep. 5 (2015) 8209.

M. Haschke, et al., Pharmacokinetics and pharmacodynamics of recombinant human angiotensin-converting enzyme 2 in healthy human subjects, Clin. Pharmacokinet. 52 (9) (2013) 783–792.

A. Khan, et al., A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome, Crit. Care 21 (1) (2017) 234.