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.

Pulmonary Pharmacology & Therapeutics 58 (2019) 101833

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Renin-angiotensin-system, a potential pharmacological candidate, in acute respiratory distress syndrome during mechanical ventilation

Di Wang[a], Xiao-qing Chai[a,*], Costan G. Magnussen[b,c], Graeme R. Zosky[b,d], Shu-hua Shu[a], Xin Wei[a], Shan-shan Hu[e]

[a] 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
[b] Menzies Institute for Medical Research, College of Health and Medicine, University of Tasmania, Hobart, 7001, Tasmania, Australia
[c] Research Centre of Applied and Preventive Cardiovascular Research, University of Turku, Turku, 20520, Finland
[d] School of Medicine, College of Health and Medicine, University of Tasmania, Hobart, 7001, Tasmania, Australia
[e] 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 $<$ $PaO_2/FIO_2 \leq$ 300 mm Hg), moderate (100 mm Hg $<$ $PaO_2/FIO_2 \leq$ 200 mm Hg), or severe ($PaO_2/FIO_2 \leq$ 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 (V_t) and high peak airway pressure (P_{peak}) increased the risk of development of ARDS both the ICU (odds ratio 2.6 for $V_t >$ 700 mL and 1.6 for $P_{peak} >$ 30 cm H2O) and during surgical ventilation (odds ratio 1.56 for each mL/kg increase of intraoperative V_t) [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

* Corresponding author.
E-mail address: xiaoqingchai@163.com (X.-q. Chai).

https://doi.org/10.1016/j.pupt.2019.101833
Received 20 April 2019; Received in revised form 24 June 2019; Accepted 31 July 2019
Available online 01 August 2019

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 V_t to avoid lung alveoli over-distension as well as a higher positive end-expiratory pressure (PEEP) at end expiration, are employed to minimize the impact of injurious ventilation [10,14,15]. However, there have been few improvements in patient outcomes in recent decades and no pharmacological therapies have been developed that have been shown to be beneficial in large-scale, randomized, controlled clinical trials (RCTs).

However, recent 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 is 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 decapeptide 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 systemically 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 in blood pressure homeostasis and cardiovascular function (as shown in Figure-1). Interestingly, AT2R is normally induced by activation of the ACE2/Ang-(1–7)/MasR axis, while more 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, Wosten-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, Jerng and colleagues found that AT1R expression, measure 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 hyperoxia-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 showed 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).

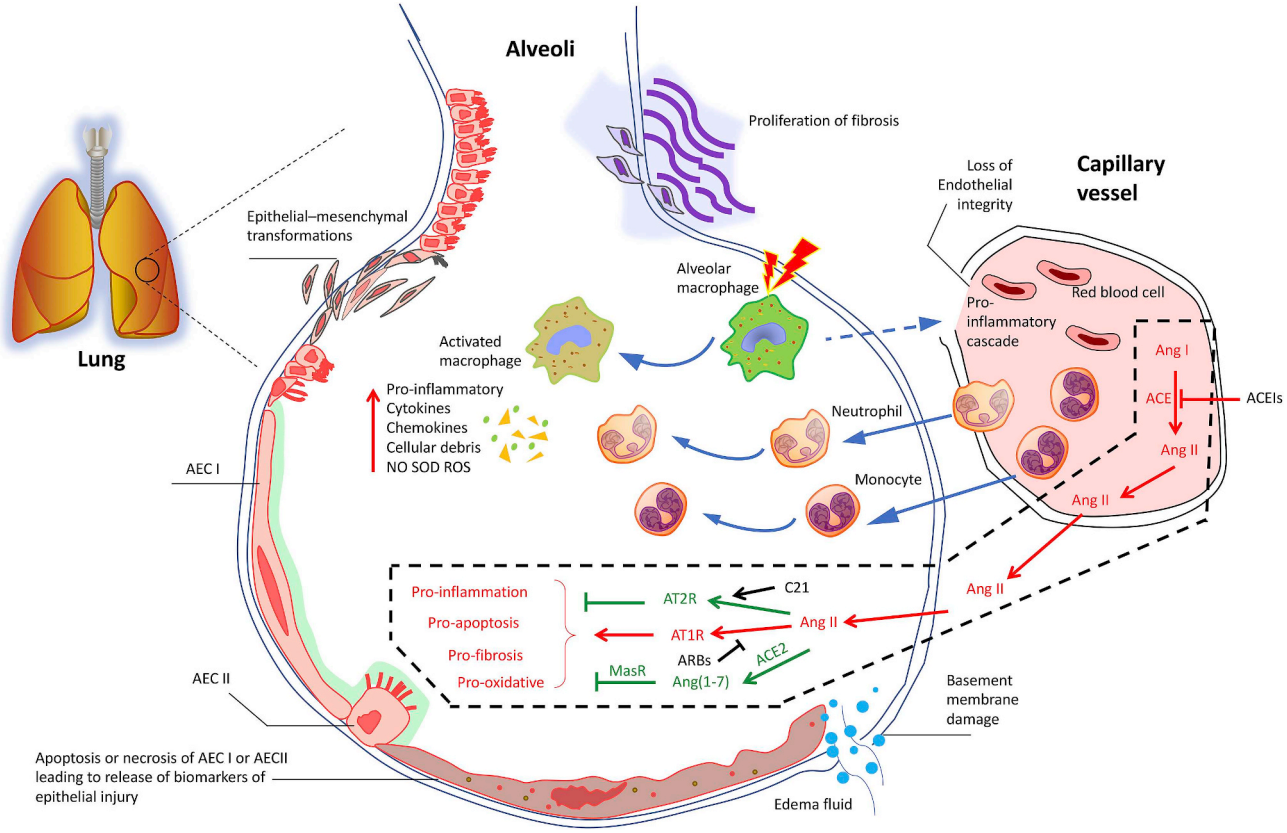

Fig. 1. Overview of RAS components within ARDS. Pathologically, ARDS is characterized by inflammatory cell infiltration in the lungs, loss of the epithelial and endothelial integrity, increased capillary permeability, and interstitial pulmonary edema and fibrosis. Ang-II, which locates at a core position in RAS, is originated from upstream Ang-I by ACE. Since ACE is expressed abundantly in the entire pulmonary capillary network, considerable amount of Ang-II enters lung alveoli when ARDS occurs. Ang-II combines with AT1R or AT2R, both of which expressed in AECs and inflammatory cells in alveoli, exerting opposing effects. Overall, Ang-II/AT1R promotes inflammatory cells activation and recruitment, induces pulmonary AECs and PVMECs apoptosis, leading to increased microvascular permeability and loss of epithelial and endothelial integrity. Conversely, AT2R activation functionally attenuates inflammation, improves AECs and PVMECs survival, reduces lung fibrosis and collagen accumulation, resulting in improved lung function and oxygenation. Besides, Ang-II is further metabolized into downstream Ang-(1–7) by ACE2. Angiotensin-(1–7) combines with MasR to antagonize Ang-II/AT1R effect, thus functionally similar to AT2R.
Abbreviations: renin-angiotensin system (RAS), acute respiratory distress syndrome (ARDS), angiotensin converting enzyme (ACE), angiotensin converting enzyme 2 (ACE2), angiotensin-(1-7) [Ang-(1-7)], AT1R blockers (ARBs), compound 21 (C21), angiotensin type 1 receptor (AT1R), angiotensin type 2 receptor (AT2R), alveolar epithelial cells (AECs), pulmonary microvascular endothelial cells (PVMECs), Mas receptor (MasR), nitric oxide (NO), superoxide dismutase (SOD), reactive oxygen species (ROS)

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 *Agtr2*-knockout 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

Table 1
Summary for evidence of renin-angiotensin system (RAS) pharmacological agents in the prevention of acute respiratory distress syndrome (ARDS) and ventilator-induced lung injury (VILI).

	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 [49]
	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 hypertension 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	Alleviation of lung edema, inflammation and fibrosis, improvement of survival of PVMECs, inhibition of proliferation of lung fibroblasts [61]
	Ang-(1–7)	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 [60]
	rhACE2	LPS induced-ARDS model	rhACE2 reversed the ACE2/ACE imbalance and increased Ang-(1–7) levels, thus reducing LPS-induced apoptosis and inflammation of PVMECs [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 [68]

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 (PVMECs), lipopolysaccharide (LPS).

ACE2 plays a beneficial role in lung injury and, potentially, ARDS.

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 [61–63]. The mechanisms of the beneficial effects on outcomes in these models include inhibition of apoptosis in AECs and pulmonary microvascular endothelial cells (PVMECs), 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 PVMECs 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) [60] or Ang-(1–7) [61] can reduce lung injury. Conversely, inhibiting MasR aggravates ARDS [62]. Based on encouraging data from experimental models, GSK2586881, a rhACE2 which has been shown to up-regulate Ang-(1–7) in Phase I clinical trials [67], has progressed to Phase II testing. In these placebo-controlled trials, administration of a broad range of doses of the drug to patients with ARDS resulted in a rapid decrease in Ang-II and up-regulation of Ang-(1–7) without significant haemodynamic effects [68]. While only preliminary (and non-significant), there was also some evidence to suggest a decrease in IL-6 levels [68] indicating that this is an intervention that is worth pursuing in the future for the treatment of ARDS.

5. Conclusion

Multiple components of the RAS have been implicated, directly and indirectly, in the pathogenesis of VILI and ARDS. There is growing evidence that the ACE/Ang-II/AT1R axis, which promotes the injury and fibrosis, plays a dominant role in the pathogenesis of VILI and ARDS, while the ACE2/Ang-(1–7)/MasR axis exerts anti-inflammatory and anti-fibrotic effects. Given the lack of effective pharmacologic treatments for ARDS, the patho-physiological role of RAS in VILI and ARDS is an area that warrants further investigation. It's quite common

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 promis 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 Natural Science Foundation (No.1608085QH210), 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) 788–800.
[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. Brodie, 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. Famous, 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. Kashiouris, 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] R.M. Wosten-van Asperen, et al., Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist, J. Pathol. 225 (4) (2011) 618–627.
[13] R.M. Wosten-van Asperen, et al., Ventilator-induced inflammatory response in lipopolysaccharide-exposed rat lung is mediated by angiotensin-converting enzyme, Am. J. Pathol. 176 (5) (2010) 2219–2227.
[14] N. Acute Respiratory Distress Syndrome, et al., Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome, N. Engl. J. Med. 342 (18) (2000) 1301–1308.
[15] M. Briel, et al., Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis, J. Am. Med. Assoc. 303 (9) (2010) 865–873.
[16] M. Wenz, et al., Angiotensin II formation and endothelin clearance in ARDS patients in supine and prone positions, Intensive Care Med. 26 (3) (2000) 292–298.
[17] J.S. Jerng, et al., Role of the renin-angiotensin system in ventilator-induced lung injury: an in vivo study in a rat model, Thorax 62 (6) (2007) 527–535.
[18] R.M. Wosten-van Asperen, et al., ACE mediates ventilator-induced lung injury in rats via angiotensin II but not bradykinin, Eur. Respir. J. 31 (2) (2008) 363–371.
[19] A. Benigni, P. Cassis, G. Remuzzi, Angiotensin II revisited: new roles in inflammation, immunology and aging, EMBO Mol. Med. 2 (7) (2010) 247–257.
[20] S. Vukelic, K.K. Griendling, Angiotensin II, from vasoconstrictor to growth factor: a paradigm shift, Circ. Res. 114 (5) (2014) 754–757.
[21] M.C. Chappell, Emerging evidence for a functional angiotensin-converting enzyme 2-angiotensin-(1-7)-MAS receptor axis: more than regulation of blood pressure? Hypertension 50 (4) (2007) 596–599.
[22] R.A. Santos, et al., Angiotensin-converting enzyme 2, angiotensin-(1-7) and Mas: new players of the renin-angiotensin system, J. Endocrinol. 216 (2) (2013) R1–R17.
[23] P.E. Walters, T.A. Gaspari, R.E. Widdop, Angiotensin-(1-7) acts as a vasodepressor agent via angiotensin II type 2 receptors in conscious rats, Hypertension 45 (5) (2005) 960–966.
[24] S.N. Patel, et al., Angiotensin II type 2 receptor and receptor mas are colocalized and functionally interdependent in obese zucker rat kidney, Hypertension 70 (4) (2017) 831–838.
[25] R. Metzger, et al., Heterogeneous distribution of angiotensin I-converting enzyme (CD143) in the human and rat vascular systems: vessel, organ and species specificity, Microvasc. Res. 81 (2) (2011) 206–215.
[26] I.V. Balyasnikova, et al., Monoclonal antibodies to native mouse angiotensin-converting enzyme (CD143): ACE expression quantification, lung endothelial cell targeting and gene delivery, Tissue Antigens 67 (1) (2006) 10–29.
[27] R.S. Wiener, et al., Angiotensin converting enzyme 2 is primarily epithelial and is developmentally regulated in the mouse lung, J. Cell. Biochem. 101 (5) (2007) 1278–1291.
[28] M. Wenz, et al., Inhaled nitric oxide does not change transpulmonary angiotensin II formation in patients with acute respiratory distress syndrome, Chest 112 (2) (1997) 478–483.
[29] K.C. Doerschug, et al., Renin-angiotensin system activation correlates with microvascular dysfunction in a prospective cohort study of clinical sepsis, Crit. Care 14 (1) (2010) R24.
[30] R.P. Marshall, et al., Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. 166 (5) (2002) 646–650.
[31] M. Adamzik, et al., ACE I/D but not AGT (-6)A/G polymorphism is a risk factor for mortality in ARDS, Eur. Respir. J. 29 (3) (2007) 482–488.
[32] J.S. Jerng, et al., Polymorphism of the angiotensin-converting enzyme gene affects the outcome of acute respiratory distress syndrome, Crit. Care Med. 34 (4) (2006) 1001–1006.
[33] A.E. Tsantes, et al., Effect of angiotensin converting enzyme gene I/D polymorphism and its expression on clinical outcome in acute respiratory distress syndrome, Minerva Anestesiol. 79 (8) (2013) 861–870.
[34] Y. Imai, et al., Angiotensin-converting enzyme 2 protects from severe acute lung failure, Nature 436 (7047) (2005) 112–116.
[35] M. Podowski, et al., Angiotensin receptor blockade attenuates cigarette smoke-induced lung injury and rescues lung architecture in mice, J. Clin. Investig. 122 (1) (2012) 229–240.
[36] Z. Zou, et al., Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections, Nat. Commun. 5 (2014) 3594.
[37] R. Wang, et al., Angiotensin II induces apoptosis in human and rat alveolar epithelial cells, Am. J. Physiol. 276 (5) (1999) L885–L889.
[38] X. Li, H. Rayford, B.D. Uhal, Essential roles for angiotensin receptor AT1a in bleomycin-induced apoptosis and lung fibrosis in mice, Am. J. Pathol. 163 (6) (2003) 2523–2530.
[39] J.S. Jiang, et al., Angiotensin-converting enzyme inhibitor captopril attenuates ventilator-induced lung injury in rats, J. Appl. Physiol. 102 (6) (1985) 2098–2103 2007.
[40] M. Papp, et al., Angiotensin receptor subtype AT(1) mediates alveolar epithelial cell apoptosis in response to ANG II, Am. J. Physiol. Lung Cell Mol. Physiol. 282 (4) (2002) L713–L718.
[41] Y. Wang, et al., Regulation of the angiotensin II-p22phox-reactive oxygen species signaling pathway, apoptosis and 8-oxoguanine-DNA glycosylase 1 retrieval in hyperoxia-induced lung injury and fibrosis in rats, Exp. Ther. Med. 13 (6) (2017) 3397–3407.
[42] C. Li, et al., Losartan, a selective antagonist of AT1 receptor, attenuates seawater inhalation induced lung injury via modulating JAK2/STATs and apoptosis in rat, Pulm. Pharmacol. Ther. 45 (2017) 69–79.
[43] S. Yao, et al., Losartan attenuates ventilator-induced lung injury, J. Surg. Res. 145 (1) (2008) 25–32.
[44] C. Chen, et al., Losartan attenuates microvascular permeability in mechanical ventilator-induced lung injury in diabetic mice, Mol. Biol. Rep. 41 (2) (2014) 809–814.
[45] S. Hagiwara, et al., Antagonist of the type-1 ANG II receptor prevents against LPS-induced septic shock in rats, Intensive Care Med. 35 (8) (2009) 1471–1478.

[46] 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.
[47] L. Shen, et al., Losartan prevents sepsis-induced acute lung injury and decreases activation of nuclear factor kappaB and mitogen-activated protein kinases, Shock 31 (5) (2009) 500–506.
[48] S. Asmussen, 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.
[49] 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.
[50] 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.
[51] M. Konigshoff, et al., The angiotensin II receptor 2 is expressed and mediates angiotensin II signaling in lung fibrosis, Am. J. Respir. Cell Mol. Biol. 37 (6) (2007) 640–650.
[52] 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.
[53] 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.
[54] 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.
[55] S.R. Tipnis, 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.
[56] 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.
[57] 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.
[58] 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.
[59] R.M. Wosten-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.
[60] G.J. Rey-Parra, et al., Angiotensin converting enzyme 2 abrogates bleomycin-induced lung injury, J. Mol. Med. (Berl.) 90 (6) (2012) 637–647.
[61] N. Klein, et al., Angiotensin-(1-7) protects from experimental acute lung injury, Crit. Care Med. 41 (11) (2013) e334–e343.
[62] 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.
[63] 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.
[64] 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) (2018) L1015–L1027.
[65] 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.
[66] 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-kappaB pathways, Sci. Rep. 5 (2015) 8209.
[67] 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.
[68] 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.