Adrenomedullin and COVID-19

Subjects: Infectious Diseases
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The COVID-19 pandemic is still in progress, and a significant number of patients have presented with severe illness. Recently introduced vaccines, antiviral medicines, and antibody formulations can suppress COVID-19 symptoms and decrease the number of patients exhibiting severe disease. However, complete avoidance of severe COVID-19 has not been achieved and there are insufficient methods to treat it. Adrenomedullin (AM) is an endogenous peptide that maintains vascular tone and endothelial barrier function. The AM plasma level is markedly increased during severe inflammatory disorders, such as sepsis, pneumonia, and COVID-19, and associated with its prognosis. Exogenous AM administration reduced inflammation and related organ damage in rodent models. The results strongly suggest that AM could be an alternative therapy for COVID-19. Researchers are currently conducting an investigator-initiated phase 2a trial for moderate to severe COVID-19 using AM.

Keywords: adrenomedullin ; translational study ; clinical trial ; COVID-19 ; pneumonia

1. Introduction

The novel coronavirus disease (COVID-19) pandemic is sweeping the globe, and it is impossible to foresee how it might end. Over five million patients have died before the end of 2021 [1]. Recently introduced vaccines, oral antiviral medicines, and antibody formulations can suppress COVID-19 symptoms and decrease the number of patients with severe conditions [2][3][4][5][6]. However, complete avoidance of severe conditions has not been achieved, and there are insufficient treatment methods for severe conditions [7]. For example, neutralizing monoclonal antibody (LY-CoV555) plus remdesivir was found to be ineffective in hospitalized patients with COVID-19 [8]. Therefore, it is still critical to determine how to save the lives of patients with severe conditions. In particular, patients who require mechanical ventilation for exacerbated pneumonia due to COVID-19 have a high mortality rate [9][10]. Severe pneumonia cannot be treated with antiviral drugs only, and alternative approaches are needed. Innovative drugs to alleviate tissue damage in severe COVID-19 cases using a different approach from conventional antiviral drugs are being investigated.

Adrenomedullin (AM) is a vasodilatory bioactive peptide that exhibits anti-inflammatory and tissue-protective actions. AM plasma concentration has been shown to increase remarkably in patients with sepsis and severe pneumonia. AM acts as an endogenous defensive substance [11][12][13][14][15][16][17][18][19][20][21][22][23]. Exogenous administration of AM has been shown to improve organ damage caused by sepsis and pneumonia in experimental animals [24]. Additionally, AM prevented ventilator-induced lung injury (VILI) in a mouse pneumonia model [25]. Mechanical ventilation worsened lung injury, which then caused multi-organ failure, including the liver, kidneys, and intestinal tract. However, AM administration in mice considerably decreased lung injury and suppressed liver and intestinal tract disorders [25]. AM decreases tissue injury by improving cytokine control and the barrier function of endothelial cells. Contrarily, AM plasma concentration and related proAM fragments were shown to increase in patients with COVID-19, and more importantly, the increase in AM was closely related to the prognosis of patients with COVID-19 [26][27][28][29][30][31][32][33][34][35][36]. These data suggest that AM plays an important role in COVID-19 pathophysiology; thus, it could be a candidate alternative treatment for COVID-19. Therefore, researchers investigated whether AM could reduce organ damage in patients with severe pneumonia caused by COVID-19 and whether it could improve patient prognosis. **Figure 1** illustrates the current therapeutic drugs for treating COVID-19 in Japan. According to Japanese guidelines, patients grouped in the moderate 1 category have pneumonia or dyspnea but do not need oxygen support, while those in the moderate 2 category require supplemental oxygen. Patients classified as having the severe form of the disease receive ventilatory support and/or are admitted to the intensive care unit (ICU). Major therapeutics in the early and mild phases of COVID-19 are sufficient, but there are limited or only partially effective treatments in the advanced phase. AM is a promising candidate for COVID-19; however, it is currently uncertain whether it plays a significant role in the advanced state of the disease.

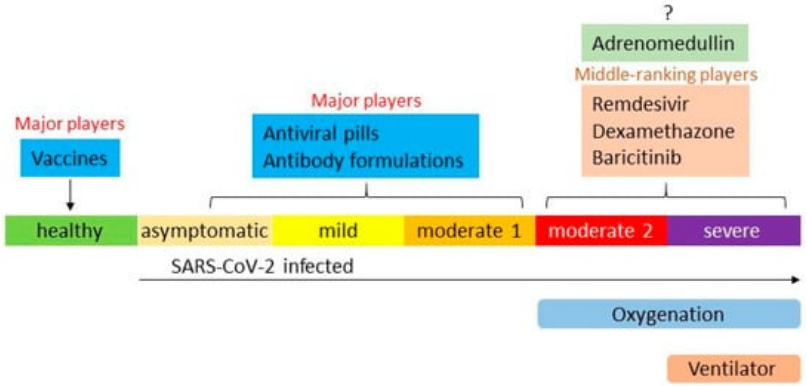

Figure 1. Current COVID-19 therapeutics, including adrenomedullin, under investigation in clinical trials.

2. Biosynthesis of AM and Its Receptors

AM, a 52-amino acid peptide, has a ring structure with a disulfide bond and an amidated C-terminal Tyr [37]. The ring structure and the amidated C-terminus are essential for bioactivity. Calcitonin (CT), the α- and β-calcitonin gene-related peptide (CGRP), amylin and adrenomedullin 2 (also known as intermedin) share structural features, namely, an amidated C-terminus and an N-terminal disulfide bond [38][39]. Therefore, these peptides, including AM, belong to the CT/CGRP superfamily [38][39]. **Figure 2** illustrates the AM synthesis process. First, a precursor consisting of a 185-amino acid peptide, designated preproAM, is synthesized and then processed into proadrenomedullin (proAM). ProAM is further processed into four segments: proAM N-terminal 20 peptide (PAMP)-Gly, mid-regional proadrenomedullin (MR-proADM), AM-Gly, and C-terminal proAM [37]. Initially processed PAMP and AM contain an additional C-terminal Gly, and these intermediate forms are biologically inactive. The intermediate forms of the peptides are enzymatically converted into the amidated C-terminal, resulting in the mature bioactive forms; however, a limited part of the peptides is converted [40]. MR-proADM is biologically inactive but stable in the bloodstream, and thus, MR-proADM can serve as a useful biomarker for AM synthesis [41].

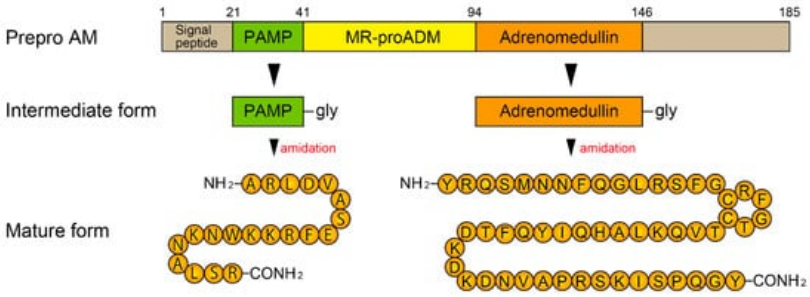

Figure 2. Biosynthesis of adrenomedullin. AM: adrenomedullin; PAMP: pro-adrenomedullin N-terminal 20 peptide; MR-proADM: mid-regional pro-adrenomedullin.

The CT/CGRP family, including AM, act on G protein-coupled receptors (GPCRs), namely the calcitonin receptor (CTR), and calcitonin receptor-like receptor (CLR). CTR can function on its own, but CLR requires the presence of chaperone molecules, called receptor activity-modifying proteins (RAMPs). AM and CGRP receptors are composed of CLR and three RAMP forms (1, 2, and 3). CLR with RAMP1 yields CGRP receptor, CLR with RAMP2 yields the functional AM receptor (AM1 receptor), and CLR with RAMP3 yields another functional AM receptor (AM2 receptor) [42]. The crucial role of AM and the AM1 receptor axis for vascular homeostasis has been clarified in experiments using knockout (KO) models, where AM KO mice developed lethal vascular abnormalities at mid-gestation resulting in extreme hydrops [43][44]. Interestingly, CGRP KO mice were normal, and only RAMP2 KO caused lethal abnormalities similar to those in the AM KO mice [45][46]. Moreover, the AM2 receptor is important in lymph vessel function [47].

3. AM and Sepsis

Several studies have provided useful information on AM in sepsis, one of the most severe infection states; the results suggest that AM is closely related to pathophysiology of sepsis and septic shock [24]. AM and MR-proADM plasma concentrations can markedly increase in patients with sepsis and septic shock, depending on the severity of the disease. More importantly, increased AM or MR-proADM levels are useful predictors in sepsis and septic shock prognosis [11][12][13][14][15][16][17][18][19][20][21][22][23]. A meta-analysis has shown that AM and MR-proADM exhibit high sensitivity and specificity

as prognostic sepsis markers with 95% confidence interval values of 0.83 (95% CI: 0.79–0.87) and 0.90 (95% CI: 0.83–0.94), respectively [48]. The close relationship between AM and sepsis suggests that AM is a crucial factor in sepsis.

AM and AM receptors are ubiquitously expressed in the body, including the heart, lungs, kidneys, adrenal glands, and intestines [49]. In particular, high AM expression has been confirmed in the vasculature, in which it is expressed in the endothelium and vascular smooth muscle cells [50]. The main function of AM in the vasculature is the maintenance of vascular tone and integrity. AM is one of the strongest vasodilators among the vasoactive peptides [51] and maintains vascular tone through direct action on vascular smooth muscle cells and nitric oxide produced in the endothelium [52][53]. More importantly, it directly stabilizes endothelial barrier function and suppresses further pro-inflammatory impairment of the vessel wall [54]. Sepsis and subsequent septic shock cause excessive vasodilation and breakdown of vascular integrity, contributing to organ damage and mortality. The early sepsis hyperdynamic phase progresses to the late hypodynamic state, causing organ damage and mortality. AM is crucial in causing the hyperdynamic phase but delays the transition to the hypodynamic state [55], the key point of the organ-protective effect of AM, even though it is a vasodilative peptide. Contrarily, vascular endothelial dysfunction is an important process in tissue inflammation, in which the loss of endothelial barrier integrity results in extravasation of fluids and molecules, causing edema and inflammation, and finally, tissue dysfunction [56][57].

Table 1 summarizes the selective effects of AM on experimental sepsis and septic shock. Genetic intervention AM models have demonstrated that AM is an endogenous protective factor against sepsis [58][59][60]. Exogenous AM administration can prevent this process and protect organs in experimental sepsis and septic shock models [25][61][62][63][64][65][66][67][68]. Although endogenous AM levels are increased in sepsis, the additional administration of exogenous AM prevents organ damage and improves the survival rate in animal models [25][61][62][63][64][65][66][67][68]. In particular, AM significantly decreases vascular, alveolar, and intestinal epithelial permeability, an essential factor in organ protection [25][62][63][67]. Based on the reported experimental models, **Figure 3** illustrates a simplified cascade of AM functions as an organ-protective factor against sepsis. Although AM is induced by bacterial endotoxin as an endogenous protective factor [69], the quantity produced is insufficient to alleviate the disease. Therefore, exogenous AM administration can be beneficial in sepsis. Unfortunately, its effects have not yet been studied and approved for patients with sepsis, and its effects on patients are unknown.

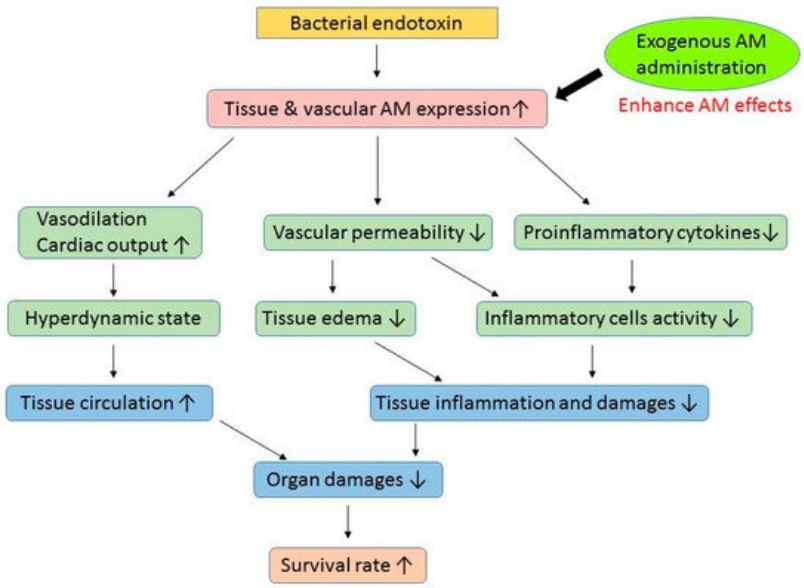

Figure 3. Simplified adrenomedullin cascade, an organ-protective factor against sepsis. AM: adrenomedullin.

Table 1. The effects of adrenomedullin on septic models.

Genetic Intervention			
Animal	**Procedure**	**Results**	**Reference**
Mouse	**AM-deficient (+/−) + LPS-endotoxemia**	**compared to WT mice · ↑ mortality · ↑ liver dysfunction**	**[58]**
Mouse	**AM-deficient (+/−) + LPS-endotoxemia**	**compared to WT mice · ↑ TNF-α, IL-1β · ↑ liver dysfunction**	**[59]**

Mouse	**AM transgenic + LPS-endotoxemia**	**compared to WT mice · ↓ BP decline · ↓ organ damage · ↑ survival rate**	**[60]**
Exogenous Adrenomedullin Administration			
Animal	**Procedure**	**Effects**	**Reference**
Mouse	**Pneumococcal pneumonia + Mechanical ventilation**	**· ↓ VILI (pulmonary permeability↓) · ↓ liver and gut injury**	**[25]**
Rat	**BDL + CLP (obstructive jaundice + polymicrobial sepsis)**	**· ↓ tissue injury and inflammatory responses · ↑ survival rate**	**[61]**
Rat	**Staphylococcus aureus α-toxin induced septic shock**	**· ↓ translocation of dextran from the gut into the systemic circulation**	**[62]**
Rat	**Cecal ligation and puncture (CLP)**	**· ↓ tissue injury · ↓ proinflammatory cytokine levels · ↓ intestinal-barrier dysfunction · ↑ survival rate**	**[63]**
Sheep	**Endotoxin (LPS) infusion**	**· ↑ cardiac index · ↓ mean pulmonary artery pressure**	**[64]**
Rat	**Endotoxin (LPS) injection**	**· ↑ PPER-γ level · ↓ TNF-α**	**[65]**
Rat	**Intestinal ischemia/reperfusion**	**· ↓ lung injury · ↓ proinflammatory cytokines**	**[66]**
Rat	**Staphylococcus aureus α-toxin induced septic shock**	**· ↓ vascular hyperpermeability · ↑ survival rate**	**[67]**
Rat	**Intestinal ischemia/reperfusion**	**· ↓ inflammatory cytokines · ↓ tissue injury · ↑ survival rate**	**[68]**

AM: adrenomedullin, LPS: lipopolysaccharide, WT: wild type. TNF: tumor necrosis factor, IF: interferon, BP: blood pressure. VILI: ventilator induced lung injury, BDL: common bile duct ligation. PPER: peroxisome proliferator-activated receptor.

4. Adrecizumab and Sepsis

Adrecizumab is a non-neutralizing humanized high-affinity antibody directed against the AM N-terminus. Adrecizumab binds to AM to form a large molecule; this modification protects the bound AM from proteolytic enzymes and results in a longer AM half-life in the bloodstream. The plasma concentration of AM in humans markedly increases and lasts for a long time after adrecizumab administration [70]. Interestingly, the MR-proADM plasma concentration has not been shown to increase with adrecizumab administration; therefore, AM biosynthesis was not shown to increase by adrecizumab [70]. More importantly, the AM N-terminus is unrelated to its bioactivity. Therefore, the adrecizumab antibody is expected to enhance the beneficial effects of endogenous AM in patients with high AM plasma levels. Adrecizumab reduces vascular leakage and organ dysfunction and improves survival in several sepsis models [71][72][73]. Based on these data, a phase 2a clinical trial of adrecizumab in septic shock patients was conducted [74]. Unfortunately, this trial did not demonstrate a definitive benefit of adrecizumab in septic shock [74]. The mechanisms of septic shock are complex, and it is a difficult target for clinical trials. For example, a meta-analysis has shown that the clinical relevance of a metabolic resuscitation cocktail (thiamine, ascorbic acid, and hydrocortisone) for sepsis is questionable [75]. Alterations to the trial protocol for adrecizumab may be needed in future trials.

5. Overview of Therapies for COVID-19

Great efforts in the development of therapeutic drugs against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been concentrated after the beginning of the COVID-19 pandemic. To start, vaccination is the most effective way to control pandemic diseases. In particular, the mRNA-based vaccine, BNT16b2, produced by Pfizer Inc. and BioNTech SE was 95% effective in preventing COVID-19 [76]. Additionally, BNT16b2 was 94% effective for preventing hospitalization and 92% effective for preventing severe disease [77]. Researchers believed that the mRNA vaccine would end the COVID-19 pandemic. However, this hope was dashed by the emergence of SARS-CoV-2 variants, such as Delta

[78] and the recent Omicron variant [79]. It has become clear that a vaccine alone cannot end COVID-19. A second method of mitigating disease is antibody formulations against SARS-CoV-2. The neutralizing monoclonal-antibody combination agent (bamlanivimab plus etesevimab) reduced 70% of COVID-19–related hospitalizations or deaths [5]. However, this combination was less effective for the Gamma variant [80], and thus antibody formulations have the same problem that vaccines do for controlling variants of SARS-CoV-2. The most recent developments are oral antiviral drugs for SARS-CoV-2 [3][4]. Pfizer's paxlovid, with 89% effectiveness, especially, may be a game changer in the treatment of COVID-19. Another anti-viral pill, molnupiravir, is also useful for patients with COVID-19, but this pill should be administered within 5 days of the onset of symptoms [81]. Remdesivir is the first approved antiviral agent, and is being used as a standard care drug for mild to severe disease caused by COVID-19. However, the benefit of remdesivir may be questionable [8], and the World Health Organization (WHO) recommendation guidelines for its use are weak or conditional [82].

Vaccines, antibody formulations, and orally bioavailable antiviral drugs are all generally useful for preventing severe illness caused by COVID-19; however, a certain proportion of patients with COVID-19 will develop severe disease, where these agents do not aid in recovery. The immune system overreaction is crucial in the progression of the acute pneumonia and resulting multiorgan damages in severe COVID-19. Therefore, immune suppression, such as that provided by corticosteroids, is effective in advanced stages of COVID-19. However, at the same time, avoidance of superimposed infection is also important with immunosuppressant therapy [83]. Significant decreases in the mortality rates of hospitalized patients with COVID-19, most of whom had moderate to severe pneumonia, were confirmed in well-organized clinical trials with dexamethasone or tocilizumab [84][85]. The benefit was clear but the differences in death at 28 days between active treatment vs. standard care were small (dexamethasone; 22.9% vs. 25.7%, rate of risk ratio 0.83, tocilizumab; 31% vs. 35%, rate of risk ratio 0.85) [84][85]. The benefit of baricitinib for hospitalized COVID-19 patients was also confirmed in a randomized, double-blind clinical trial [86]. This trial included patients with mild to moderate COVID-19, and the composite primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28. The difference between baricitinib and placebo was also small: 27.8% vs. 30.5% (odds ratio 0.85) [86]. The superiority of combination therapy, namely, baricitinib plus remdesivir compared with remdesivir alone, for hospitalized COVID-19 patients was also reported [87]. This trial enrolled patients with moderate (68.3%) and severe (31.7%) illness where everyone was administered remdesivir and additionally received baricitinib or placebo. The primary outcome measure was the time to recovery during the 20 days after enrollment. The median time to recovery (95% CI) was 7 days (6–8) in the baricitinib group and 8 days (7–9) in the placebo group (rate ratio 1.16, $p = 0.03$) [87]. The mortality rate over the entire trial period was 5.1% in the baricitinib group and 7.8% in the placebo group, and the hazard ratio for death was 0.65 (95% CI, 0.39 to 1.09) [87]. These trials have demonstrated significant but partial benefits of immune modulators for moderate to severe pneumonia caused by COVID-19.

Abnormalities of coagulation and disseminated intravascular coagulation (DIC) are noticeable characteristics of COVID-19 and anti-coagulation therapy is crucial for the treatment of advanced stages of COVID-19. D-dimer is the representative marker for coagulation abnormalities and thus the marker for the prognosis of patients with advanced COVID-19 [88]. However, advanced COVID-19 is a complicated disease and a single marker, such as D-dimer, to detect coagulation abnormalities is insufficient [89]. DIC associated with COVID-19 is very different from that of septic DIC, and both thrombotic and hemorrhagic pathologies should be noted [90]. Thrombosis treatment is essential for COVID-19, in addition to antiviral and cytokine storm treatments. Initial anticoagulant treatment with low molecular weight heparin has been shown to reduce mortality by 48% at 7 days and 37% at 28 days, which demonstrates the major impact anticoagulation therapy can have [88]. Therefore, antithrombotic prophylaxis is strongly recommended for all hospitalized patients with COVID-19, but therapeutic anticoagulation is adapted for carefully selected patients to avoid severe hemorrhagic complications [91].

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