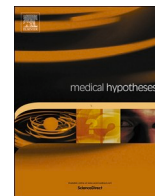




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Scientific hypothesis and rational pharmacological for the use of sacubitril/valsartan in cardiac damage caused by COVID-19

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ARTICLE INFO

Keywords:
Cardiology
Covid-19
Cytokine
Nephrilisin
Sacubitril
Sars-CoV-2

ABSTRACT

On March 11, 2020 the World Health Organization (WHO) declared the state of global pandemic caused by the new SARS-CoV-2 (COVID-19). To date, no antivirals directed against SARS-CoV-2 or effective vaccines to combat the viral infection are available. Severe acute respiratory syndrome caused by SARS-CoV-2 is treated empirically with antivirals, anti-inflammatory, anticoagulants. The approval of an effective vaccine still takes time. In this state, it may be useful to find new therapeutic solutions from drugs already on the market. Recent hypotheses suggest that the use of AT-1 receptor antagonists (ARB) in combination with neprilisin inhibitors (NEPi) could indirectly provide clinical benefits to patients with SARS-CoV-2 and cardiac involvement. In this article we investigate and describe a possible innovative pharmacological approach for the treatment of the most severe stages of COVID-19 infection.

Introduction

Clinical aspects SARS-CoV-2 (COVID-19) infection

A viral epidemic caused by a new coronavirus SARS-CoV-2 (COVID-19) began in Wuhan (China) in November 2019. The epidemic quickly turned into a global pandemic in March 2020 [1]. Knowledge of this viral infection is evolving rapidly, to date there are no direct antivirals or effective vaccines and therapeutic treatments are on empirical basis, antiviral, immunomodulators, anti-inflammatory, anticoagulants [2]. At the time of writing of this article, 1.21 Mln deaths and 47.4 Mln infected people have been reported [3]. SARS-CoV-2 is a family of RNA viruses that can infect humans and cause serious respiratory tract infections that can be fatal in some cases. Studies have shown that SARS-CoV-2 has about 80% of the SARS-CoV like genome, responsible for the 2003 outbreak [4]. SARS-CoV-2 penetrates cells using the S protein through the angiotensin 2 conversion enzyme receptor (ACE-2) on the cell surface, which is widely present in the epithelial cells of the respiratory mucosa [5]. ACE-2 is also a conversion enzyme with a key role in the renin-angiotensin (RAS) system. Clinical experts and scientists have described SARS-CoV-2 infection in three phases: the first asymptomatic or slightly symptomatic, the second moderately severe characterized by

a pulmonary inflammatory state, the third very severe phase characterized by a generalized inflammatory state affecting all tissues causing multi-organ dysfunction [6]. In the most severe stages of infection, COVID-19 lung lesions are characterized by diffuse alveolar damage with irregular inflammatory cellular infiltration consisting of monocytes, macrophages and lymphocytes infiltrating the lung tissue and the presence of intravascular thrombosis [7]. Severe inflammatory pulmonary infiltration prevents the exchange of alveolar gases, in addition, in more serious cases other organs may be damaged such as the heart or liver [8,9]. Systemic inflammation in the most severe stages of infection can cause cardiac damage such as pericarditis, acute coronary syndrome, electrophysiological disorders and the appearance of arrhythmias. These aspects are further confirmed by studies showing that patients with a history of cardiovascular disease are at increased risk of COVID-19 complications [10]. In fact, in a recent study [11] it was found that 77% of deceased patients developed acute myocardial damage [12]. Some molecular and pathophysiological bases have been hypothesized, one of which is that the phenomenon of “cytokinetic storm” [13,14] that occurs in the most severe stages of COVID-19 infection causes myocarditis which is the cause of acute heart failure, TNF- α and some other pro-inflammatory cytokines are able to induce typical cellular modifications of the decompensated heart, such as down-

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regulation of the sarcoplasmic ATPase calcium pump [15], or decoupling of beta-adrenergic receptors from activation of cyclic intracellular AMP [16] or death of cardiac cells.

Cytokinic storm and heart failure

The most severe stages of COVID-19 infection are characterized by a hyperinflammatory state caused by a cytokinic storm. The term indicates a massive and sudden release of cytokines that generate an uncontrolled and generalized inflammatory response [17–19] causing organ damage. The data clearly indicate an uncontrolled and sudden release by immune effector cells of large amounts of proinflammatory cytokines such as IFN α , IL-1 β , IL-6, IL-12, IL-18, IL-33, TNF- α , TGF- β [20] and chemokines such as CXCL10, CXCL8, CXCL9 [21–24]. An increase in pro-inflammatory cytokines in particular may be responsible for cardiac damage. Several studies show that TNF- α plays a central role in myocardial contractility depression through various time-dependent mechanisms. The cardiodepressant effect of TNF- α is the consequence of a signaling dependent on nitric oxide synthase (NOS), a high concentration of nitric oxide (NO) leads to [25] an inotropic negative effect [26] and a profound systolic and diastolic dysfunction [27]. TNF- α also induces apoptosis in cardiac myocytes [28], which contributes to the thinning of the left ventricular wall [29,30]. At molecular level, sustained overexpression of TNF- α activates both intrinsic and extrinsic apoptotic pathways and leads to progressive loss of antiapoptotic proteins [31]. IL-6 is a powerful mediator of myocardial depression, which in turn improves the cardiodepressant effects of TNF- α and IL-1 [32]. The inotropic negative effect of IL-6 is the result of JAK2/STAT3 mediated activation of iNOS [33]. IL-1 also produces a prolonged decrease in myocardial contractility [34]. Finally IL-18 stimulates proinflammatory cytokines with known cardiodepressant effects, i.e., TNF- α , IL-1 α , IL-1 β , IL-6, and also IL-18 has been shown to induce the synthesis of NO, which mediates myocardial dysfunction. In addition, cardiac damage induced by COVID-19 may further intensify a local inflammatory reaction and excessive production of reactive oxygen species (ROS). Finally, through different mechanisms of action, the proinflammatory cytokines described above mediate contractile dysfunction and myocytic cardiac apoptosis with cardiac damage (Figs. 1 and 2) [35,36].

Natriuretic peptide system, biological effects

Natriuretic peptides are a family of structurally related hormonal factors. Atrial natriuretic peptide (ANP) and type B natriuretic peptide (BNP) are secreted by the atria and cardiac ventricles. Type C natriuretic peptide (CNP) is the most highly expressed natriuretic peptide in the brain, but is also highly expressed in chondrocytes and endothelial cells. Neutral neprilisin endopeptidase (NEP) is the enzyme that metabolizes natriuretic peptides. Natriuretic peptides mediate different physiological effects through interaction with specific guanylyl cyclase receptors (GC) that stimulate intracellular cGMP production. The main physiological effects are natriuresis / diuresis and peripheral vasodilation, inhibition of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). Recent evidence associates natriuretic peptides with other important functions, in particular, some studies have demonstrated an antifibrotic and anti-inflammatory action. The natriuretic peptide type C (CNP), a member of the family of natriuretic peptides, through selective binding to the transmembrane receptor guanylyl cyclase (GC)-B, mediates different biological effects in various organs [37]. CNP is expressed in a wide variety of tissues, such as vascular endothelium, heart, bones and adrenal glands [38–41]. CNP plays an important role in the regulation of local vascular tone and has been shown to have mainly cardioprotective, antihypertrophic [42] and antifibrotic [43] effects. Recently, CNP has been shown to have protective effects against inflammatory and fibrotic reactions [44,45]. Tests *in vivo* have revealed that CNP attenuates acute lipopolysaccharid-induced lung lesions (LPS) [46]. CNP also regulates the secretion of inflammatory cytokines [47,48]. In the inflammatory phase, expression levels of various chemokines, cytokines and growth factors are high and these mediators exert their profibrotic activity through the activation and proliferation of fibroblasts [49]. Considering the pathophysiological importance of fibroblast activation in pulmonary fibrosis [50], and the above mentioned biological effects, it is suggested that there is a direct effect on pulmonary fibroblasts by natriuretic peptides. These insights suggest the use of therapeutic agents that increase the concentration of these peptides in the most severe stages of COVID-19 infection when a fibrotic pulmonary state and a cardiac fibrotic tissue is present. In association with evidence of antihyperproliferative effects, the studies also show direct antifibrotic effects mediated by the action of natriuretic

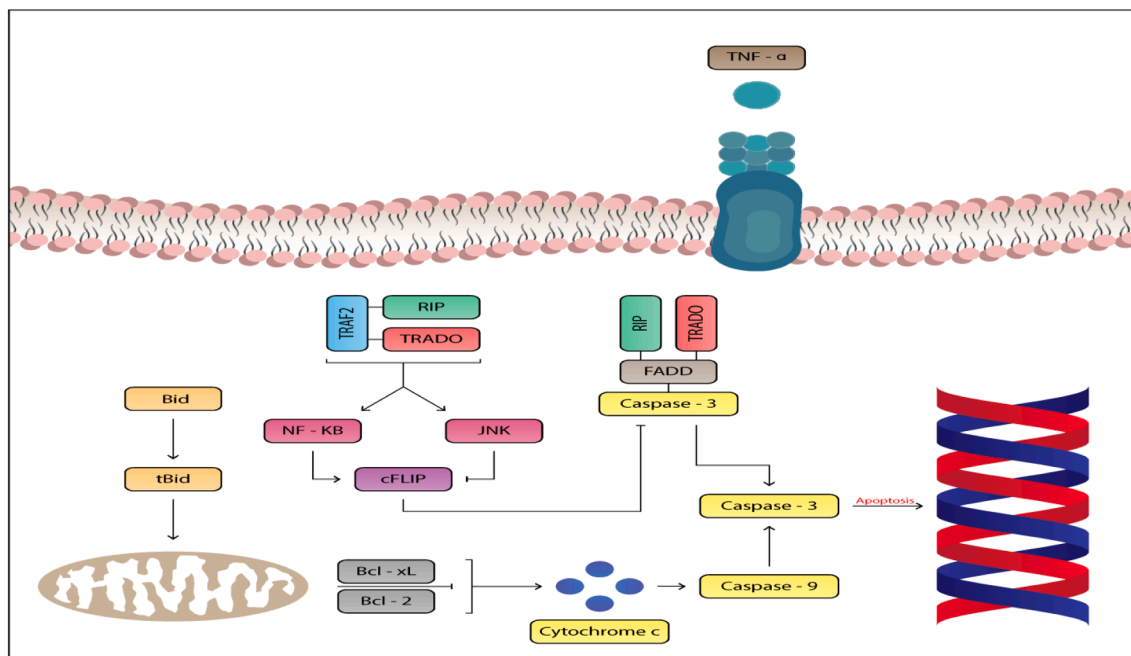


Fig. 1. The proinflammatory cytokine TNF-alpha can induce apoptosis of cardiac myocytes inducing cardiac damage.

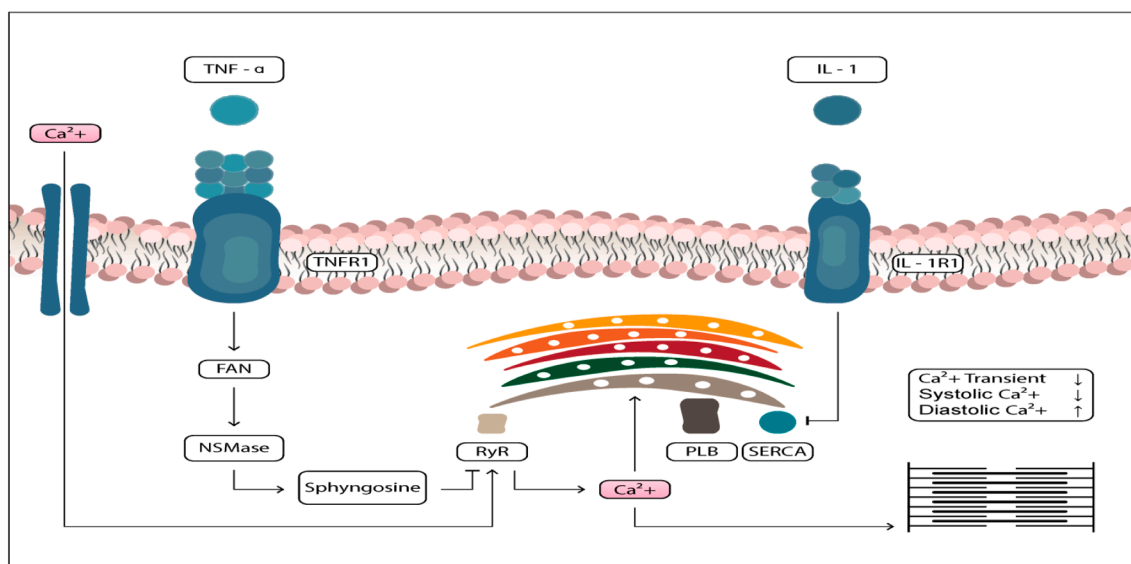


Fig. 2. Pro-inflammatory cytokine IL-1 mediates inotropic negative effect and contractile cardiac dysfunction.

peptides. In particular, some studies associate the peptide BNP with an important inhibitory effect on NALP3 the activation of inflammation, which is related to the BNP-induced reduction of NF- κ B and ERK1/2 activation. The data indicate a powerful anti-inflammatory and immunomodulatory role for this peptide [51]. These mediated effects described above suggest that natriuretic peptides may play an important role in COVID-19 infection.

NT-proBNP in patients with severe COVID-19

BNP is synthesized as a prohormone (proBNP), upon release into the bloodstream it is divided in equal proportions into biologically active BNP and biologically inactive NT-proBNP. Stress and myocardial damage are the main release stimuli for BNP and NT-proBNP, studies have shown that increased cytokines and an inflammatory state are important additional factors inducing hormone secretion [52]. BNP is degraded by plasma through endopeptidase neprilisin (NEP), NT-proBNP is excreted primarily by renal excretion. BNP and NT-proBNP are important biomarkers for the evaluation of cardiac function [53,54]. As described above, cardiac lesions are a common condition among patients hospitalized with COVID-19. A recent study has shown that the NT-proBNP marker has increased significantly in more severe cases of COVID-19, suggesting a relationship between high plasma levels of NT-proBNP, cardiac damage, and risk of death in patients with severe COVID-19. The explanation for the increase in NT-proBNP in severe COVID-19 is probably due to cardiac complications resulting from up-regulation of the sympathetic and angiotensin system (RAS), cytokinic cascade and systemic inflammation. In particular, cytokine storm [55,56] could probably play an important role in cardiac damage [57] and the increase of NT-proBNP. In addition, RAS overactivation with reduced ACE-2 concentration, as evidenced in the most severe stages of COVID-19 infection, may lead to increased synthesis of Ang II with proinflammatory and profibrotic effects (mediated by AT-1 receptors) that facilitates the secretion of NT-proBNP [58,59]. Pending well-structured and thorough studies, to assess whether the NT-proBNP marker can be a useful diagnostic test to assess the severity of COVID-19 infection, all the considerations expressed suggest a therapeutic pharmacological solution with the action of increasing the concentration of circulating natriuretic peptides, decrease the concentration of NT-proBNP, increase RAS via ACE-2 axis with increased synthesis of Ang 1-7 and Ang 1-9 with antifibrotic and anti-inflammatory effects, and decrease the effects of Ang II on the AT-1 receptor [60-63].

The Hypotheses/theory

Potential role of Sacubitril/valsartan

The Sacubitril/valsartan combination is the first of a new class of drugs with therapeutic indication for the treatment of symptomatic chronic heart failure with reduced ejection fraction [64]. Sacubitril is a neprilisin inhibitor (NEPi), valsartan an angiotensin II receptor antagonist (ARB). Based on the above considerations, the association sacubitril/valsartan could be an important therapeutic solution to combat COVID-19 infection and reduce cardiac induced damage. The use of the sacubitril/valsartan association could be of clinical benefit for several reasons, in particular the antagonism on the AT-1 receptor mediated by valsartan would lead to increased AT-2 receptor occupation by Ang II with antifibrotic, anti-inflammatory, antihyperproliferative and vasodilator effects with potential benefits on both lung lesions caused by fibrotic tissue and cardiac damage caused by COVID-19. In addition, the actions of Ang-II on the AT-1 receptor, which mediates vasoconstrictive, profibrotic and hyperproliferative effects, are blocked.

Finally, angiotensin II can cause increased inflammation through the production of IL-6, TNF- α and other inflammatory cytokines mediated by AT-1. [65-67] It is known that in the more severe stages of COVID-19 infection there is a decrease in ACE-2 which plays a protective role. ACE-2 synthesizes Ang 1-7 and Ang 1-9 with known anti-inflammatory, vasodilator, antifibrotic and antihyperproliferative effects [68-70]. The antagonism on AT-1 receptors by valsartan leads to a compensatory increase of ACE-2 and a higher stimulation of MAS receptors [71]. Finally, after ARB administration the response to hypertrophic growth induced by TNF- α is significantly attenuated [72] (Fig. 3). The beneficial effects of NEPi are attributable to the decrease in the degradation of natriuretic peptides. Natriuretic peptides cause vasodilation by stimulating the guanylate cyclase receptor to produce cGMP. In addition, sacubitril administration is known to decrease NT-proBNP, which in severe cases COVID-19 is increased. In patients with COVID-19, with and without symptoms attributable to pneumonia, there is evidence of a significant increase in NT-proBNP, regardless of left ventricular dysfunction. Indeed, studies show that NT-proBNP levels are also the result of acute renal lesions and pro-inflammatory molecules such as interleukin-1 and C-reactive protein [73]. In addition, natriuretic peptides act to suppress hyperactivation of the sympathetic system and decrease endothelin secretion. In addition, as mentioned above, natriuretic peptides also exert anti-inflammatory, antifibrotic and

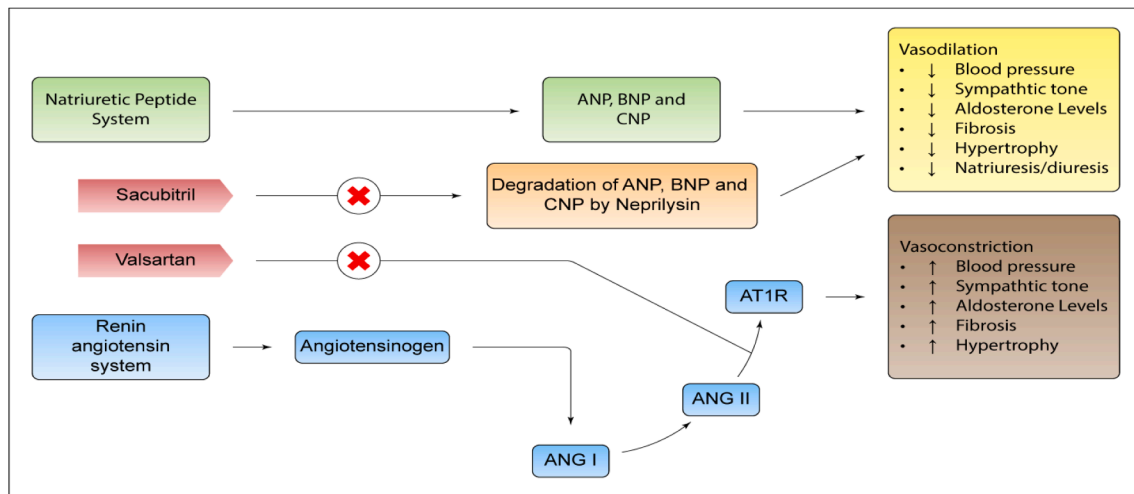


Fig. 3. Mechanism of action: Sacubitril/valsartan has the mechanism of action of neprilisin inhibitor and angiotensin II receptor blocker type-1 (AT1). The complementary cardiovascular benefits of sacubitril/valsartan are attributed to the increase in neprilisin-degraded peptides and the simultaneous inhibition of the effects of angiotensin II. Natriuretic peptides exert their effects through the activation of membrane bound receptors coupled to the enzyme guanylyl cyclase, causing an increase in concentrations of the second messenger, cyclic guanosine monophosphate (cGMP), which can lead to vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity and antihypertrophic/anti-fibrotic effects.

antihypertrophic effects. In particular, some evidence shows direct anti-inflammatory effects mediated. In particular, some studies associate the BNP peptide with an important inhibitory effect on the activation of inflammatory NALP3, which is related to the reduction of NF- κ B and ERK1/2 activation induced by BNP [74]. In addition, for this class of drugs acting on RAS, there is a potential indirect protection against SARS-CoV-2. In fact, patients with cardiovascular diseases are at high risk of pneumonia, studies show that the use of drugs that block RAS decreases this risk [75].

Conclusions

In severe COVID-19 patients, in addition to lung damage, there may be significant cardiac involvement, which is responsible for worsening the clinical condition of the host. The main cardiac manifestations can be edema, pericarditis, myocarditis, cardiac fibrosis, and impairment of contractile function and cardiac electrophysiology. Many pharmacological agents, when used appropriately, may be helpful in preserving cardiac homeostasis or reducing induced COVID-1 cardiac damage by decreasing mortality. Based on the evidence described and in relation to the hypotheses suggested by us, the use of the sacubityl/valsartan association in patients with COVID-19, especially in the most severe cases with induced cardiac damage, could be of therapeutic benefit, with cardioprotective, anti-inflammatory and antifibrotic effects that can also combat lung damage, through an increase in the natriuretic peptide system and a decrease in the effects of AT-1 receptor-mediated Ang-II. Well-structured clinical studies are needed to confirm these hypotheses.

Founds

None

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The authors certify that the manuscript is original, never submitted to other journal for publication before. All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text.

Declaration of competing interest

None of the Authors have conflicts of interest to disclose.

Acknowledgements

We would like to thank Dr. Daniel Bittencourt, graphic designer, for creating new and unpublished images for our article.

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