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Review Article

Can SARS-CoV-2 Infection Target the Key Mechanisms Responsible for TH-Induced Cardiac Hypertrophy?

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Abstract

SARS-CoV-2 recruits Angiotensin Converting Enzyme 2 (ACE2), to bind and enter into host cells with the attachment of major spike glycoprotein (S1) to the active site of ACE2, at the extracellular surface. Moreover, patients with underlying diseases that cause to increase ACE2 activity, may have a higher chance of developing severe COVID-19. According to previous studies, the level of ACEs, angiotensin II (AngII) and Ang- (1–7) is affected by insufficient or excess production of thyroid hormones. The level of ACE and AngII increases in the plasma, heart and kidney of the patient with hyperthyroidism. Then AT1R and AT2R activation contributes to T3-induced cardiac hypertrophy by activating some important pathways such as, Akt/GSK3β/mTOR, NFkB and Akt, TGF-β respectively. On the other hand, although plasma Ang-(1–7) level is consistent in the case of hyperthyroidism, cardiac ACE2 activity, Ang-(1–7) and Mas receptor protein levels increase in the heart in hyperthyroid state. Then MAS receptor activation by increased levels of Ang-(1–7) contributes to suppress the development of T3-induced cardiac hypertrophy by blocking GSK3β/NFATc3 activation. Thus, due to the cardiac ACE2 over activity in the hyperthyroidism and the role of ACE2 in the virus attachment and internalization, ACE2 level can decrease because of receptor-induced endocytosis after virus entry. Therefore, patients with underlying hyperthyroidism may be susceptible to SARS-CoV-2 infection. Moreover the concurrence of hyperthyroid state and COVID-19 may increase the risk of TH-mediated cardiac hypertrophy and heart failure because of increased AngII and decreased Ang-(1–7) and their involved mechanisms.

Keywords: SARS-CoV-2, Coronavirus, COVID-19, ACE2, Hyperthyroidism

Introduction

Up to now, seven coronaviruses have developed in human with weak or severe respiratory diseases. Some of them such as SARS-CoV-2 are responsible for multi-organ failure and cardiomyopathy in addition to respiratory problems [1]. The attachment and entry of SARS-CoV-2 into host cells is facilitated by the binding of major spike glycoprotein (S1) to the active site of angiotensin converting enzyme 2 (ACE2) at the extracellular surface [2] with higher affinity than 2002 SARS-CoV [3]. One of the mechanism proposed for virus internalization is ACE2 shedding with sheddases such as ADAM10/17 and then receptor- mediated endocytosis [1]. The Transmembrane Proximal Serine Protease 2 (TMPRSS2) have also an important role in the virus internalization with ACE2 cleaving and spike protein priming [4] (Figure 1). The overexpression of ACE2 is a natural figure of some cells in organs such as lung, esophagus, ileum and colon, skin, heart, kidney, bladder and brain. Thus, those high ACE2-expressing cells are in the potential high risk for SARS-CoV-2 infection [5]. In addition, the high expression of ACE2 in patients with severe COVID-19, compared to healthy individuals can propose that patients with such concurrent diseases that cause to increase ACE2 level may have upper probabilities of developing severe COVID-19 [6,7]. ACE2 as an important negative regulator of the Renin Angiotensin System (RAS) is a main role playing enzyme in AngII and AngI cleavage and forming angiotensin-(1–7) and angiotensin-(1–9) [3]. Studies have shown that Hypo or hyperthyroidism may affect the levels of ACEs, AngII and Ang - (1–7). In this context, in the state of hyperthyroidism the levels of renin, Ang II, AT1R and AT2R are increased in plasma , heart and kidney [8]. Then AT1R activation triggers T3-induced cardiac hypertrophy by activating the, Akt/GSK3β/mTOR, and NFkB signaling pathways and AT2R activation contributes to Akt and TGF-β activation. On the other hand, Although plasma Ang -(1–7) levels is consistent in the case of hyperthyroidism, cardiac ACE2 activity, Ang -(1–7 levels increase and hinder the development of T3-induced cardiac hypertrophy by blocking GSK3β/NFATc3 signaling pathways via the MAS receptor activation [9]. Thus, Thyroid Hormone (TH) develops cardiac growth and RAS, is a main moderator by modulating the key RAS components such as ACE2 [10] with no changes in the plasma levels of Ang- (1–7) [9]. Therefore, due to increased cardiac ACE2 activity in hyperthyroidism state and the role of ACE2 in the virus attachment and internalization, ACE2 level can decrease due to ACE2- mediated endocytosis and patients with concurrent SARS-CoV-2 infection and underlying hyperthyroidism may be susceptible to TH-mediated cardiac hypertrophy and heart failure both because of the reduction of Ang- (1–7) level and the intensification of Ang II as a result of ACE2 consumption for virus internalization (Figure 1). *The highlight of this article is saying about the two possibilities. First, people with hyperthyroidism are more likely to get the Covid-19 virus, and second, people with hyperthyroidism and infected by the virus are more likely to have cardiac hypertrophy and heart failure.*

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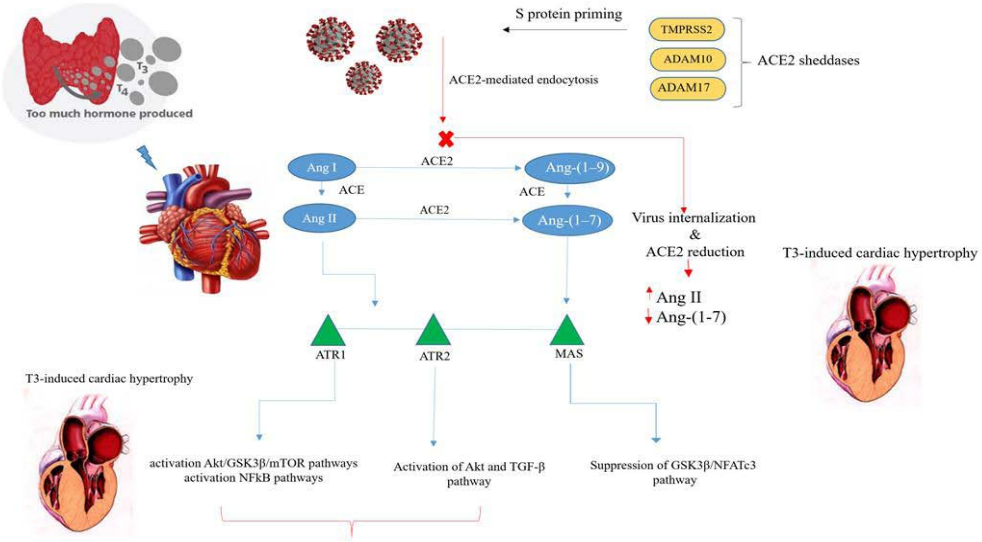

Figure 1: SARS-CoV-2 infection and the possibility of T3-induced cardiac hypertrophy. Hyperthyroidism is associated with increased level of Ang II as well as the overstimulation of AT1R and AT2R in the heart that leads to T3-induced cardiac hypertrophy. The upregulate of ACE2/Ang 1–7/Mas receptor as the main counter-regulatory mechanism can prevent heart growth. In SARS-CoV-2 infection and the process of virus internalization by ACE2-mediated endocytosis, ACE2 reduction and following increased Ang II and decreased Ang-(1-7) can trigger T3-induced cardiac hypertrophy. Three ACE2 sheddases, ADAM10/17 and TMPRSS2 contribute to ACE2 cleavage needed for virus internalization. Moreover TMPRSS2 facilitates the entry of the virus through the S protein priming.

The human coronaviruses and their cellular receptors

After the first characterization of human coronaviruses in the 1960s, up to the end of 2012 as a conservative estimate, six new human coronaviruses have been recognized such as HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV and MERS-CoV [1,11]. The novel coronavirus, SARS-CoV-2, at the end of 2019 is responsible for respiratory infections increasing with the presence of underlying diseases. The spike proteins of HCoV-NL63, SARS-CoV and SARS-CoV-2 recruit ACE2 as a cellular receptor [1] but the affinity of SARS-CoV-2 is 10–20-fold higher than SARS-CoV [3]. Thus ACE2-expressing cells, such intestine, heart, skin, lung and kidney are susceptible to SARS-CoV-2 infection(5).With regard to MERS-CoV, a multifunctional serine peptidase, dipeptidyl peptidase 4 (DPP4)/CD26) is a role-playing protein in cellular attachment [1]. HCoV-229E uses the human Aminopeptidase N (hAPN) as its receptor but the receptors for HCoV-HKU1 and HCoV-OC43 are currently unknown [12]. *The highest affinity to ACE2 by SARS-Cov-2 is highlighted message in this section.*

ACE2 receptor and its performance in modulating renin-angiotensin system

ACE2 as a member of the ACE family with active site on the extracellular surface, has considerable homology to Angiotensin-Converting Enzyme (ACE). Angiotensin II (ANGII) is generated as a result of Angiotensin I (ANGI) cleavage by ACE. Moreover angiotensin Type 1 Receptor (AT1R) activation and following vessels constriction and blood pressure elevation is the result of ANGII binding. ACE2 acts as a negative regulator of the renin-angiotensin system, with a dual performance which leads to vasoconstriction modulations. ACE2 makes ANGII inoperative by converting it to angiotensin-(1–7) as well as splitting ANGI into angiotensin-(1–9). Then ACE act as a convertor of angiotensin-(1–9) to angiotensin-(1–7) with vasodilator effect when attaching to Mas receptor. On the other hand, ANGII has a negative control role on ACE2 by overexpression of metalloproteinase ADAM metallopeptidase domain 17 (ADAM17) which can break and release ACE2. Angiotensin Type I Receptor (AT1R) also can upregulate ADAM17 and help more cleavage of ACE2 [13]. It is due to a physical tendency of AT1R and ACE2 to make complexes. In the presence of excess Ang II, the separation of AT1R and ACE2 complexes on the cell surface can trigger over expression of ADAM17 and the following internalization and degradation of ACE2 by lysosomes [3].

SARS-CoV-2 cellular internalization

After SARS-CoV-2 - ACE2 attachment , the internalization of the virus may start with two separate mechanisms: ACE2 cleavage and shedding to promote virus entry, and cleavage of the spike to promote membrane fusion [14]. With regard to, ACE2 cleavage, the ACE2 sheddases, ADAM17 [2], ADAM10 [1], and the Transmembrane Proximal Serine Protease 2 (TMPRSS2) are functional proteins and compete to cleave the receptor [3,14]. Moreover TMPRSS2 facilitates the entry of the virus through the S protein priming [13]. The less ACE2 available, the less ANGII degradation and the more AT1R stimulation can cause Acute Respiratory Distress Syndrome (ARDS) and myocardial injury [3] (Figure 1).

Molecular changes after viral infection

According to miRNAs role in the regulation of various cellular activities such immune responses [15,16], results from small miRNA profiling showed strong upregulation of miRNA-155 as an inflammation regulator [17] after Sars-Cov and SARS-CoV-2 infection in lung and gut cell lines [18]. One of the leading mechanisms for organ failure in Covid-19 is the cytokine storm, containing pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) [19]. In addition, Interferon Regulatory Factors (IRFs) trigger the upregulation of

nuclear factor-κB (NF-κB). It is worth nothing that inhibition of the HSP90 chaperone activity by Tanespimycin/17-N-allylamino-17-demethoxygeldanamycin (17-AAG) leads to drop of viral replication, and downregulation of TNF-α and IL-1B genes [18].

ACE2 expression in hyperthyroidism-induced cardiac hypertrophy

Several studies have shown that there is the crosstalk between Thyroid hormone and the RAS in different tissues and over activation of thyroid gland leads to increase the levels of cardiac renin, Ang II, AT1R and AT2R [8,9]. AT1R and ATR2 activation causes T3-mediated cardiac hypertrophy by stimulating the miR-208a/α-MHC, Akt/GSK3β/mTOR, NFkB pathways as well as Akt and TGF-β activation respectively. Moreover, an overexpression of Ang-(1–7), ACE2 activity and the MAS receptor in the heart with no variations in the plasma have been shown in the case of hyperthyroidism. Augmented levels of Ang-(1–7) inhibits the development of T3-induced cardiac growth via the MAS receptor activation and its blocking effect on GSK3β/NFATc3 signaling pathways [9]. Thus, hyperthyroidism can upregulate ACE2/Ang 1–7/Mas system as the main counter-regulatory mechanism in the TH-mediated cardiac hypertrophy [20] (Figure 1). *This highlights that hyperthyroidism increases ACE2 expression, and it leads to cardiac hypertrophy.*

Discussion

SARS-CoV-2 with high genome phylogenetic resemblances to the human SARS-CoV recruits the similar receptors, ACE2, for the attachment and internalization to the host cells. Heart, brain, oral and nasal mucosa, nasopharynx, kidney, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver and blood vessels are the main ACE2 expressing organs with high potential to SARS-CoV-2 infection [7]. One of the proposed causes of cardiovascular system involvement is associated with a direct infection of Cardiomyocytes (CMCs) by SARS-CoV-2 and the expansion of myocarditis [4]. Moreover, patients with underlying heart diseases demonstrated overexpression of ACE2, and might have high possibility of SARS-CoV-2 infection and its related heart effects [21,22]. Literature studies have shown that in the hyperthyroid state, overstimulation of ACE/Ang II/AT1R axis can cause hyperthyroidism-induced cardiac hypertrophy [23]. Then the activation of the ACE2/Ang-(1-7)/Mas pathway can reduce T3-induced cardiac hypertrophy [9]. In hyperthyroid-COVID-19 patients may increase the risk of TH-mediated cardiac hypertrophy and heart failure as a result of ACE2 reduction and following increased AngII and decreased Ang-(1–7) and their involved mechanisms. Thus, SARS-CoV-2 infection can positively affect the key mechanisms responsible for TH-induced cardiac hypertrophy and develop heart failure.

Conclusion

In this context, we discuss, the augment of cardiac levels of ACE2, may provide the predisposing condition for SARS-CoV-2 infection in hyperthyroid state. Moreover, the reduction of ACE2 in the process of virus internalization, and the following increased Ang II and decreased Ang-(1-7) may develop T3-induced cardiac hypertrophy by targeting related key mechanisms. So, it is expected that people with hyperthyroidism and will be more likely to get coronavirus and develop heart failure. *Therefore, it is recommended that the hyperthyroid people take extra care against the coronavirus.*

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