



Interaction of local and systemic renin angiotensin aldosteron system with COVID-19

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ABSTRACT

Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) passes into cells through binding the angiotensin-converting enzyme-2 (ACE-2). While many scientists worldwide are trying to understand the physiopathological mechanisms of the disease and its relationship with other diseases, they are trying to find drugs that can treat Coronavirus disease-2019 (COVID-19). It is reported that the incidence of COVID-19 increases in cardiovascular diseases and associated conditions such as diabetes mellitus and hypertension in studies. That is why a large number of scientists are now questioning the use of renin-angiotensin-aldosterone system (RAS) antagonists, angiotensin-2 (Ang-2) receptor antagonists (angiotensin receptor blockers), and ACEs in COVID-19 patients. When all these facts are considered together, their potential effects may be more significant. Some researchers stated that RAS inhibitors might amplify COVID-19 severity. Per the classical knowledge, ACE-2 regulates RAS by converting Ang-2 to angiotensin-(1-7), which has antioxidant, vasodilatory, anti-inflammatory, and protective effects on many cell types, especially cardiomyocytes and vascular cells. Local and systemic RAS components such as ACE-2, ACE, and Ang-2 and their interactions are pretty complex. However, numerous reported RAS substrates and enzymes are synthesized intracellularly in many cell types. This review highlights that the intracellular RAS may have prominent roles in developing potential treatment strategies for COVID-19.

Introduction

Coronavirus disease-2019 (COVID-19) pandemic is currently the most critical health problem threatening the world. The relation of COVID-19 with renin-angiotensin-aldosterone system (RAS), especially with angiotensin-converting enzyme-2 (ACE-2), has been suggested (1). There are many pathways in the physiopathological and biochemical mechanisms of RAS that are still not understood. It is well-known that RAS plays a leading role in the initiation and progression of cardiovascular diseases. At the same time, RAS is a regulator of blood volume, pressure, and systemic vascular resistance that plays a pivotal role in the physiological and pathological responses in the cardiovascular system, such as regulating blood pressure, maintaining water and electrolyte homeostasis, vascular permeability, cellular proliferation, migration, apoptosis, intracellular signaling, angiogenesis and fibrosis (2,3). RAS contains renin, angiotensin-2 (Ang-2), Ang-2 receptors (ATRs),

ACE, and ACE-2. The most potent molecule of this system is Ang-2. As such, ACE inhibitors or ATR blockers are used to treat hypertension (HT) and chronic cardiovascular diseases. Inhibition or decrease in Ang-2 levels reduces blood pressure and causes arteriolar vasodilation by decreasing sodium and water reabsorption. Systemic endocrine effects occur when the components are produced in specific organs with enzymes and substrates and released into the bloodstream (4). However, in recent years, it has been shown that the effects of this system are not only systemic but RAS components are synthesized intracellularly in various organs and tissues. It is regulated independently from systemic RAS and has local paracrine and autocrine effects (5,6). Notably, the synthesis of Ang-2 and other substrates and enzymes of RAS [angiotensinogen, Angiotensin-1 (Ang-1), renin, ACE] occurs locally (intracellular) by many cells such as neurons, cardiomyocytes, fibroblasts, endothelium, and vascular smooth muscle cell (7). In addition,

it has been emphasized in many scientific studies that local RAS induces the acute defects and progression of various cardiovascular diseases. An increase in Ang-2 synthesis is observed in HT. Therefore, drugs to inhibit the components of this system have been developed to treat RAS-associated cardiovascular and renal diseases. Especially, ACE, AT1R (8), and renin antagonists are among the current drug therapies used in HT, heart failure, and diabetic nephropathy patients (9).

Effects of Renin-Angiotensin System

RAS components have detrimental effects on the cardiovascular system. The main components of classical RAS are:

1. Angiotensinogen, a massive globular protein,
2. Renin, which converts angiotensinogen to Ang-1 molecule,
3. ACE, an enzyme that converts Ang-1 to Ang-2, an octapeptide, membrane-dependent metalloproteinase,
4. Ang-2, basic effector peptide,
5. ATR, responsible for the cellular effects of Ang-2.

These essential components information about RAS is gradually increasing. Different ATRs (AT1R, AT2R, AT3R, AT4R) and signaling pathways arising from the activation of these receptors are defined. Ang-2 contacts with well-defined cell membrane receptors, AT1R and AT2R, and additional intracellular receptors (cytoplasmic and nucleus) (4,10). However, while rodents have two types of AT1R, humans have only one form. Conformational change occurs when it binds to the AT1R that mediates Ang-2 signal transduction. It activates phospholipase C with AT1R receptor stimulation and increment of inositol 1, 4, 5 triphosphates (IP3) and cytoplasmic (intracellular) calcium and diacylglycerol activate mitogen activator protein kinases (MAPK), extracellular signal-regulating kinases (ERK), and JAK/STAT pathway, increases protein phosphorylation. AT1R activation leads to cardiovascular remodeling (11). Binding of Ang-2 to AT1R, while Ang-2-AT1R passes quickly into the cell cytoplasm, desensitization takes place by stimulation with the agonist. As the receptor turns back to the plasma membrane, Ang-2 settles down intracellular localizations such as lysosome and cell nucleus (12). However, internalization and desensitization in AT2R do not occur. It is believed that Ang-2 has less relationship with AT2R on acute cardiovascular effects (13). These two receptor types have also been shown to have functionally opposite effects.

Meanwhile, Ang-2 shows its effects through cell proliferation, growth, formation of new vascular structures and vasoconstriction through AT1R, and the inhibition of cell proliferation and growth via AT2R. Its activation causes vasodilation and antiangiogenesis with the formation of NO and cGMP. RAS includes peptides consisting of Angiotensin-2-8 (Ang-3), Angiotensin-3-8 (Ang-4), Ang-(1-7), and Ang-(1-12) (5). The degradation of Ang-2

synthesizes Ang-(1-7) by catalytic reactions via ACE-2. It is thought that responses such as vasodilation and cytoprotective effects increased by promoting antagonist effects and thus stabilizing RAS. ACE is ordinarily a cell surface protein and is found in serum, lung, seminal fluid, and plasma (14,15). The majority of this enzyme that provides the formation of Ang-2 is found in endothelial cells. Although most of the transformation occurs during blood flow through the lungs, it is stated that this transformation occurs in many parts of the body (16). Discussions continue about the increase of vascular ACE in experimental hypertension. Vascular ACE has been shown to increase in two kidney single clip hypertensive rats, but this increase could not be confirmed in spontaneously hypertensive rats (17). It has been shown that ACE production in many living species (human, dog, and rabbit) is also in the endothelial and adventitia layer (5). After all, it has been reported that ACE concentration is high in the vascular smooth muscle cell and endothelial cell cultures. In addition to membrane-attached forms, secreted and local forms of ACE have been characterized in mesangial cells. ACE also inactivates bradykinin, a potent vasodilatory (14,18). Increased bradykinin level due to ACE inhibitors in HT causes cough in more than 20% of patients (19). ACE inhibitors have been primary care therapy for HT for years (8,20).

Coronavirus and RAS Affinity

COVID-19 is a pandemic affecting countries and millions of people that causes severe pneumonia and cardiovascular damage. Accordingly, understanding the tissue damage and underlying mechanisms caused by severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) is crucial. COVID-19 spreads over cells through one of the RAS components, ACE-2 (21). Although RAS is a complex set of mechanisms, it plays essential roles in many physiological processes involving vascular structure and remodeling. Spike protein of SARS-CoV-2 is transmitted to cells by connecting with ACE-2 membrane receptor. SARS-CoV-2 mediates tissue injury and causes an imbalanced ACE/ACE-2 ratio. In addition, ACE-2 adversely affects RAS and functions as the binding receptor for the coronavirus (2,22).

The incidence of SARS-CoV-2 increases in older people with cardiac diseases, hypertension, and diabetes mellitus (23-25). Studies have reported that the target of SARS-CoV-2 is ACE-2 in cells, which is expressed excessively in lung epithelia, small intestine, heart, and kidney in humans (14,26). ACE-2 is a membrane-involved enzyme that converts Ang-1 to Ang-(1-9) and Ang-2 to Ang-(1-7) (27), a peptide with vasodilator and antiproliferative properties (28,29). Ang-(1-7) levels were associated with several diseases, including hypertension, hypertrophic myocardial disease, myocardial infarction, chronic kidney disease. Ang-(1-7) has anti-growth and antiproliferative effects in cardiomyocytes, fibroblasts, and vascular smooth muscle cells (26,30). Thus, ACE-2 regulates RAS in the

negative direction by inhibiting Ang-2 and competing with ACE for Ang-1. ACE-2 knockout mice developed cardiomyopathy with increased pathological hypertrophy, collagenase levels, oxidative stress, inflammatory cytokines, and MAPK activation, and these signaling pathways were inhibited by angiotensin receptor blockers (ARB) (9). The expression of ACE-2 is increased in type 1 or type 2 diabetes mellitus and HT patients. These data indicate that ATRs and ACE inhibitors increase ACE-2 expression (31).

In another cohort study, it was reported that people using ACE inhibitors and ARBs had less severe disease (32). ACE-2 protein expression and activity in the heart and kidney are augmented by treatment with ACE inhibitors and ARBs differently (26). This leads to an organ-specific augmentation of local production of Ang-(1–7), as demonstrated in rats (14,31,33). As a result, the increase in ACE-2 expression would facilitate infection with COVID-19. It was hypothesized that the increase of ACE-2 synthesis augments the risk of COVID-19 infection.

Notwithstanding, although not shown in human studies or the setting of COVID-19, such potential upregulation of ACE-2 by ARBs or ACE inhibitors have caused speculation of contingently increased risk for COVID-19 course in the users of RAS blockers. However, no clinical or experimental data have demonstrated adverse or beneficial outcomes with background use of ATR blockers and ACE inhibitors or other RAS antagonists in COVID-19 patients. A recent study determined an increase in serum Ang-2 levels of COVID-19 patients. Based on this, ACE/ACE-2 balance appears to be critical inside and outside in many cell types, particularly the lung cells (34). As ACE-2 level increases following treatment with ARBs and ACE inhibitors (31,35), it is thought that the use of soluble ACE-2 in therapy may prevent the coronavirus from binding to its receptors (36). However, ACE inhibitors in practice did not inhibit ACE-2 (37). ACE-2 deficient mice do not develop lung injury following exposure to SARS-CoV-2 (38). Although these evaluations may seem to be correct on the systemic RAS, another issue to be considered is the intracellular ACE-2 production and COVID-19 connection.

Interestingly, *in vitro* works in cell lines suggested that ACE-2 is the physiological receptor for coronavirus associated with SARS-CoV-2 and acute respiratory distress syndrome (39). It is known that in diabetic conditions, cardiomyopathic hamsters show an increased intracellular ACE synthesis in cardiomyocytes (40,41). From this point of view, ACE inhibitors used today can provide ACE inhibition outside the cell. For this reason, it seems more appropriate to try drugs that can be effective by entering through the cell membrane for inhibition of ACE and ACE-2 produced into the cell. At the same time, it can be thought that intracellular RAS, which is present in many cell types other than the vascular cells, may facilitate the spread of

COVID-19 in the human body. However, it may be considered that the coronavirus binding to ACE-2 increases the penetration into the cell. After internalizing the receptor, intracellular ACE-2 level may increase when the receptor exposes to the membrane again.

Conclusion

The intracellular RAS has hidden substantial therapeutic implications and generally not inhibited by classical ARBs and ACEs. Since they do not pass into the cell and inhibit ACE and angiotensin receptors outside of the cell. Drugs that can inhibit ACE-2 internalization can be developed. Recent findings show that blockage of the local RAS might provide significant additional clinical implications in COVID-19 patients. This is consistent with recent reports that 'classical' therapeutic protocols of RAS inhibition (ARBs and ACEs blockers) might not have as much cardiovascular efficacy as anticipated. High doses of ACE inhibitors are often necessary to inhibit the RAS completely. Another issue that should be mentioned is that renin is contained in the synthesis of both local and extracellular RAS components. Thus, a renin inhibitor therapy might be an attractive therapeutic modality for conditions with intracellular RAS activation. Consequently, with the increase of molecular studies on RAS and its components, their roles in organ pathologies and the mechanisms of RAS activation at the tissue level will be revealed. In this manner, as the number of experimental practices increases, we may learn more about COVID-19 and related consequences.

Ethics

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