Clinical Infectious Diseases

CORRESPONDENCE

COVID-19 and the Renin-Angiotensin-Aldosterone System

To the Editor—I further Hanff and colleagues' [1] timely call for epidemiological and clinical investigations of coronavirus disease 2019 (COVID-19), including measurements of the renin-angiotensin-aldosterone system (RAAS) components, as substudies would be insightful of this pandemic. Angiotensin-converting enzyme 2 (ACE2) participates in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cell entry. This infection downregulates ACE2. Drugs that block RAAS also affect ACE2 expression; it is downregulated by renin inhibition and upregulated by ACE inhibitors, angiotensin receptor blockers [1], and mineralocorticoid receptor antagonists [2]. Other likely regulatory factors are age, type 2 diabetes, and sex difference [3]. These interactions would directly affect the balance between the beneficial and deleterious angiotensins (Angs), such as Ang (1–7) and Ang (1–9) vs excess Ang II. Such perturbations would also indirectly influence other RAAS components, and the coordination between circulating and local tissue expressions, as shown in Figure 1.

ACE2 is distributed throughout the body and is abundantly expressed in the lung, small intestine, and in blood vessels of many organs including the brain, heart, kidney, and testis [4]. These organs and blood vessels are potential sites of infection. The downregulation of ACE2 would reduce the production of Ang (1–7) and Ang (1–9), and concurrently prevent the reduction of Ang II, tilting the balance to Ang II accumulation that may lead to toxicity [1] (Figure 1B). Such dysregulation likely contributed to reported cases of acute respiratory distress syndrome [1], inflammation, myocardial injury [5], neurological incidences [6], and gastrointestinal manifestations [7].

Other components and the crosstalk between the systemic circulation and local tissue renin-angiotensin system would also be disrupted. Changes in circulating Ang II concentration alter renin secretion through a negative feedback loop (Figure 1A); as Ang II decreases, renin secretion increases and consequently affects renin concentration and plasma renin activity (PRA). Renin converts angiotensinogen to Ang I and PRA is a measure of this rate. Renin catalytic activity is enhanced when bound to its receptor (PRR) [8]. The inhibition of renin or ACE reduces circulating Ang II with an increase in renin concentration. It is conceivable that circulating renin could bind to PRR, where expressed, and activate the local tissue renin-angiotensin system. Ang II changes would also affect aldosterone stimulation and Ang IV production. Ang IV through its receptor AT_4 has opposite biological effects to Ang II via receptor AT_1. We therefore suggest the measurement [9] of potential affected RAAS components, Ang (1–7), Ang (1–9), Ang II, circulating ACE2, and PRA, from which Ang I can be derived. Such results would characterize the impact of the COVID-19 infection on the RAAS.

Notes

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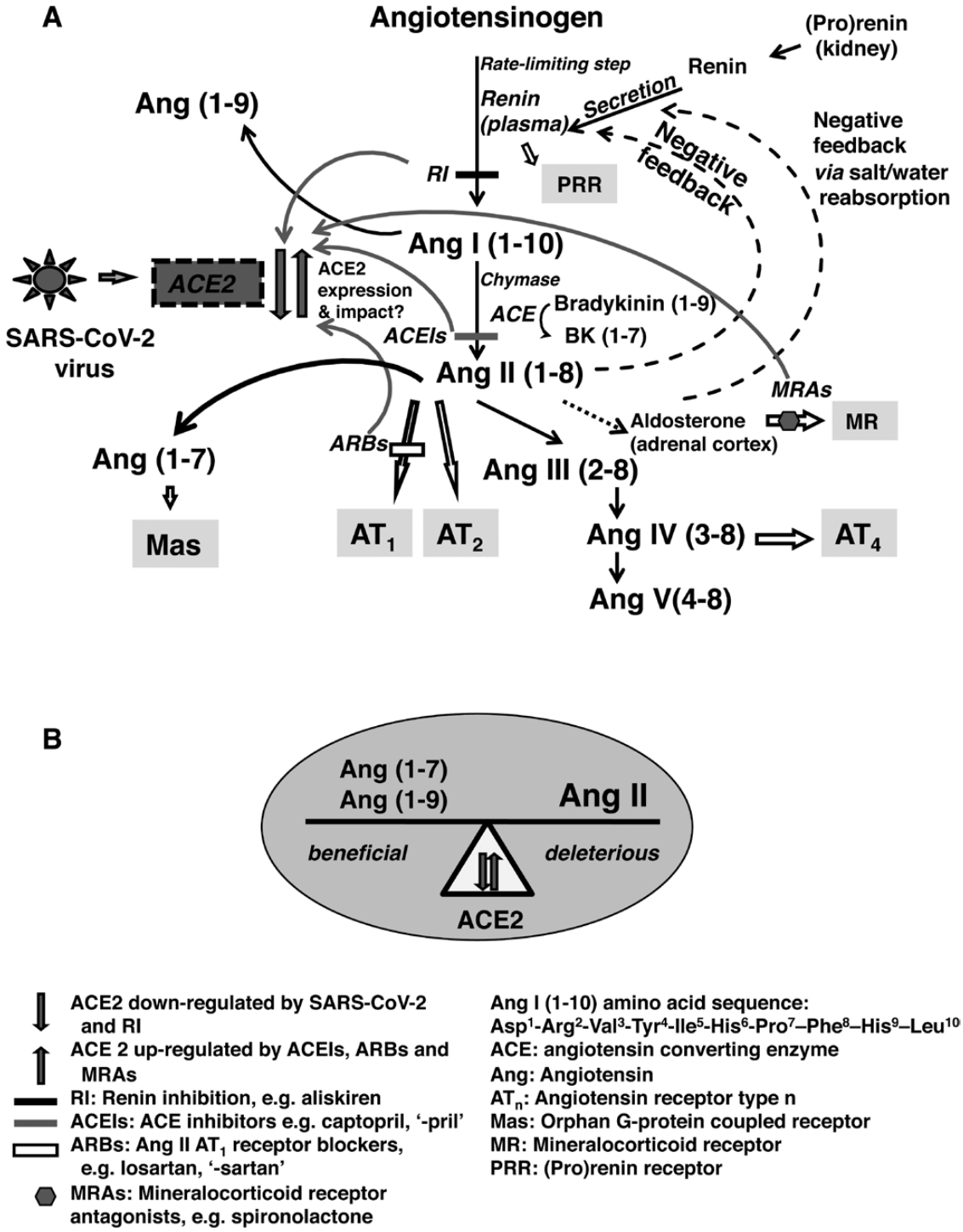

Figure 1. Flow diagram showing the renin-angiotensin-aldosterone system (RAAS) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and points of RAAS drug blockade (*A*) and implications of angiotensin-converting enzyme 2 (ACE2) perturbations on directly affected angiotensins (Angs) (*B*). Changes in ACE2 expression would impact the beneficial, deleterious, and other components of the RAAS. Physiologically, the RAAS maintains blood pressure and body water balance. ACE2 is downregulated by SARS-CoV-2 infection and renin inhibition (RI), and upregulated by angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). Renin is secreted from the kidney, which transforms angiotensinogen to Ang I, the rate-limiting step. Circulating renin can also bind to (pro)renin receptor (PRR) with likely activation of the local tissue renin-angiotensin system throughout the body. Ang I is converted to Ang II by ACE and by a second enzyme, chymase. ACE also converts bradykinin (1–9) to bradykinin (1–7) [Bk (1–7)]. Ang II is further transformed to Ang III, Ang IV, and Ang V. A negative feedback loop controls Ang II concentration changes with renin secretion that responds in the opposite direction. Ang II stimulates the release of aldosterone. However, excessive Ang II is deleterious and is associated with hypertension, congestive heart failure, and chronic kidney disease. ACE2 transforms Ang I and Ang II, that is, Ang I to Ang (1–9), and Ang II to Ang (1–7). Ang (1–9) and Ang (1–7) have protective effects balancing the deleterious Ang II, when in excess.