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ORAL DISEASES WILEY

LETTER TO THE EDITOR

Renin–angiotensin II–aldosterone axis in SARS-CoV-2-associated xerostomia

Coronaviruses, including the etiological agent responsible for the COVID-19 pandemic, SARS-CoV-2, utilize the receptor, angiotensin I converting enzyme 2 (ACE2), on the human host cell surface to gain entry into cells. The high-affinity interaction of SARS-CoV-2 spike (S) glycoprotein with ACE2 is suspected to be responsible for the efficient human-to-human transmission and the rapid global spread of the disease (Shang et al., 2020). ACE2 is essential and sufficient for cellular entry of the virus, as soluble extracellular domain of ACE2 or antibodies that target the receptor binding motif can effectively block viral entry. Structural studies suggest that murine and rat receptors interact less efficiently with the S protein than human receptors, and transgenic expression of human ACE2 promotes virus entry in murine cells (Wan, Shang, Graham, Baric, & Li, 2020), providing further evidence that cellular entry of SARS-CoV-2 depends on human ACE2.

Xerostomia is one of the most common oral manifestations in COVID-19 patients (Chen, Zhao, et al., 2020; Díaz Rodríguez, Jimenez Romera, & Villarroel, 2020). Major salivary glands contribute to 90% of total salivary flow, and their compromised function causes xerostomia. Unlike intestines, testis, gallbladder, renal tubules, and heart where high ACE2 expression can be consistently validated across mRNA and protein datasets (Sungnak et al., 2020), its expression in major salivary glands is low or undetectable (Uhlen et al., 2015; Human Protein Atlas). Although it is conceivable that, similar to the upper airway epithelium, ACE2 is expressed in a small subset of salivary gland cells, the reversal of hyposalivation with the

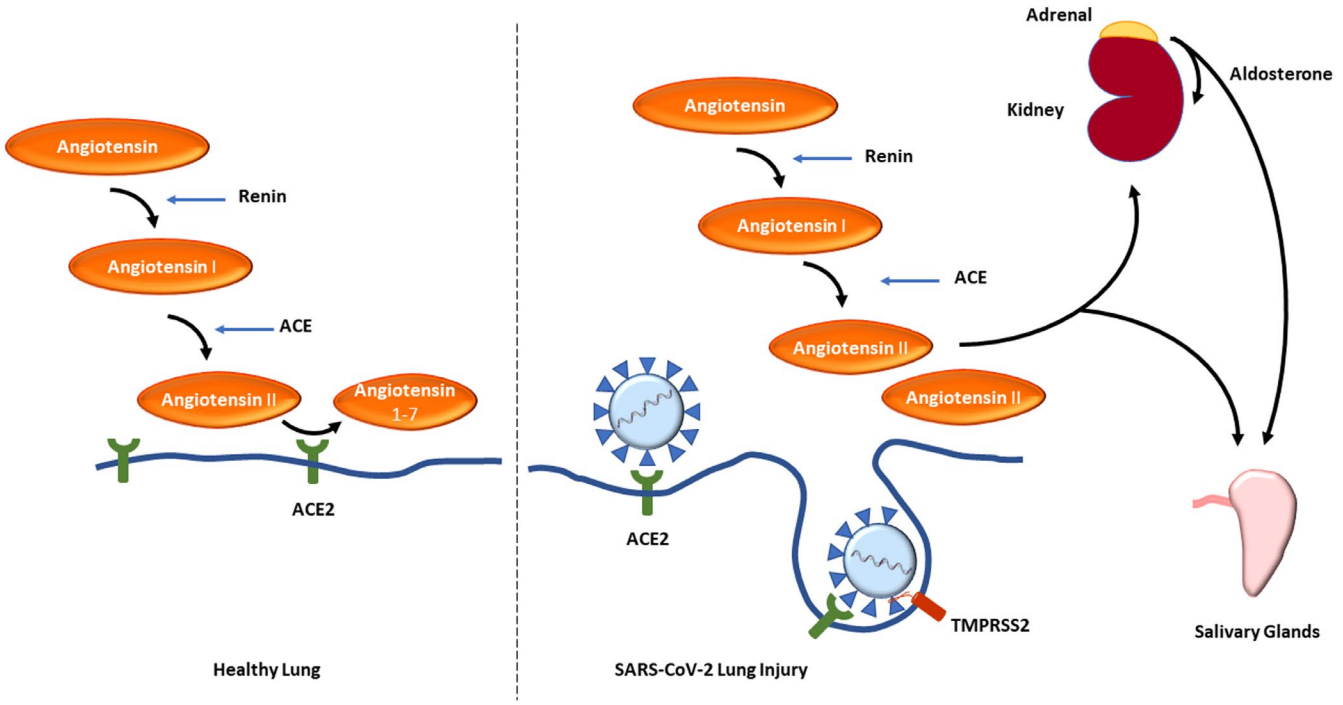

FIGURE 1 The potential mechanism of SARS-CoV-2-associated xerostomia. The RAS is a hormonal cascade that functions to regulate among others, blood pressure, and sodium–potassium balance. The potent vasoconstrictor, angiotensin II, is the primary physiological product of RAS that is counter-regulated by angiotensin 1–7 formed through cleavage by ACE2. SARS-CoV-2 occupancy of ACE2 and its limited cell surface availability leads to increase in serum angiotensin II and release of aldosterone from the adrenal glands. Vasoconstriction, hypertension, and sodium and water retention by the salivary glands result in xerostomia

resolution of COVID-19 argues against virus-mediated destruction of salivary glands as the underlying etiopathology. An alternative hypothesis for xerostomia in COVID-19 patients is the downstream pathophysiological effect of overactivation of the renin–angiotensin system (RAS) caused by the virus. The primary effector of RAS is the vasoconstrictor angiotensin II, and ACE2 plays a crucial role in counter-regulating the effects of angiotensin II by converting it to angiotensin 1–7 (Figure 1). By regulating the level of angiotensin II, ACE2 opposes vasoconstriction, sodium retention, inflammation, and fibrosis.

As utilization and sequestration of ACE2 receptors by coronaviruses alter their surface availability, there occurs an imbalance of circulating angiotensin II, leading to the release of aldosterone from the adrenal glands. Aldosterone action on distal tubules and collecting ducts of the kidneys causes sodium to be reabsorbed and potassium to be excreted in the urine. Salivary gland ductal cells respond to aldosterone by reabsorbing sodium and, indirectly, water. The net effect of high levels of angiotensin II and aldosterone is an increase in extracellular fluid, vasoconstriction, hypertension, and hypokalemia. The SARS-CoV-2–RAS interplay is suggested to be responsible for the common comorbidities of COVID-19, including hypokalemia and hypertension (Chen, Li, et al., 2020), and it could also explain the finding of xerostomia in patients.

SARS-CoV-2 mRNA can be readily isolated from pharyngeal sputum, but it could be isolated from submandibular gland saliva only in critically ill patients (Chen, Zhao, et al., 2020), suggesting a relationship with acute viremia. Although poor microcirculation due to SARS-CoV-2-induced endotheliitis (Varga et al., 2020) or virus neurotropism in causing xerostomia cannot be discounted (da Silva Pedrosa, Sipert, & Nogueira, 2020), studies that assess the therapeutic benefits of RAS correction in COVID-19 patients could help discern the pathobiology of xerostomia and, by extension, taste acuity.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

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