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MINI REVIEW ARTICLE

How SARS-CoV-2 might affect potassium balance via impairing epithelial sodium channels?

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Abstract

Severe acute respiratory syndrome coronaviruses 2 (SARS-CoV-2) is the causative agent of current coronavirus disease 2019 (COVID-19) pandemic. Electrolyte disorders particularly potassium abnormalities have been repeatedly reported as common clinical manifestations of COVID-19. Here, we discuss how SARS-CoV-2 may affect potassium balance by impairing the activity of epithelial sodium channels (ENaC). The first hypothesis could justify the incidence of hypokalemia. SARS-CoV-2 cell entry through angiotensin-converting enzyme 2 (ACE2) may enhance the activity of renin–angiotensin–aldosterone system (RAAS) classical axis and further leading to over production of aldosterone. Aldosterone is capable of enhancing the activity of ENaC and resulting in potassium loss from epithelial cells. However, type II transmembrane serine protease (TMPRSS2) is able to inhibit the ENaC, but it is utilized in the case of SARS-CoV-2 cell entry, therefore the ENaC remains activated. The second hypothesis describe the incidence of hyperkalemia based on the key role of furin. Furin is necessary for cleaving both SARS-CoV-2 spike protein and ENaC subunits. While the furin is hijacked by the virus, the decreased activity of ENaC would be expected, which causes retention of potassium ions and hyperkalemia. Given that the occurrence of hypokalemia is higher than hyperkalemia in COVID-19 patients, the first hypothesis may have greater impact on potassium levels. Further investigations are warranted to determine the exact role of ENaC in SARS-CoV-2 pathogenesis.

Keywords Electrolytes · Serum potassium · Hypokalemia · Hyperkalemia · COVID-19 · SARS-CoV-2 · 2019-nCoV · Epithelial sodium channels · ENaC

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Introduction

The current pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronaviruses 2 (SARS-CoV-2) have affected more than 191 million people worldwide with a total mortality of 4.1 million as of 23 July 2021 [1].

Electrolyte abnormalities are common manifestations of the disease and are substantially attributed to poor prognosis [2, 3]. Recently, the prevalence of mild hypokalemia (serum potassium < 3.5, > 3 mmol/L) and severe hypokalemia (serum potassium < 3 mmol/L) were estimated to be 37% and 18%, respectively, in patients with COVID-19 [4] and it was significantly associated with intensive care units admission and requirement of invasive mechanical ventilation [5]. On the other hand, hyperkalemia was determined to occur in 10.3% of patients and it was associated with increased risk of 30-day mortality [6]. Therefore, the high prevalence of potassium disorders may have a potential relationship with the natural history of SARS-CoV-2. Understanding and investigating the clinical manifestations of COVID-19 could provide insights into the pathophysiological features of this emerging virus. As a result, we will review the current literature on the roles of renin–angiotensin–aldosterone system (RAAS) and epithelial Na^+ channels (ENaC) on serum potassium levels affected by SARS-CoV-2 infection.

SARS-CoV-2 and RAAS

The coronavirus spike protein plays a fundamental role in the early stages of the SARS-CoV-2 infection, which contains a S1 domain responsible for receptor binding and a S2 domain mediating membrane fusion [7]. The S1-spike protein interacts with angiotensin-converting enzyme 2 (ACE2), a part of the RAAS, which is known as a multi-hormonal system, having a profound impact on the maintenance of electrolyte balance and blood pressure regulation [8, 9]. The RAAS is defined as a two-arm, counter-regulatory system and is divided into classical and alternative axes [10].

In the classical axis, Angiotensin I (Ang I) is generated by the cleavage of a precursor peptide called angiotensinogen, and then is converted to Angiotensin II (Ang II) by ACE [10]. Ang II attaches to Ang II type 1 receptors (AT1R) and as a result, the ACE/Ang II/AT1R axis induces acute lung failure and also triggers aldosterone release from the adrenal gland [11, 12]. Along this pathway, Ang II activates Ang II type 2 receptors (AT2R), which have the opposite effects to Ang II/AT1R and acts to resolve inflammation, but AT2R expression is significantly lower during the human lifespan, except at the neonatal stage [10, 13].

In the alternative axis, RAAS is balanced by ACE2, which is a homologue of ACE [14]. ACE2 can transform Ang II to Angiotensin 1–7 (Ang 1–7) and convert Ang I to Angiotensin 1–9, which can be further converted to Ang 1–7 [10]. Ang 1–7 is a specific Mas receptor (MasR) agonist and plays a central role in the alternative axis of the RAAS, ACE2/Ang 1–7/MasR [10]. Binding Ang 1–7 to MasR exerts several protective effects, such as antioxidative, antiinflammatory, and antifibrotic effects, in addition to decreasing aldosterone secretion [15, 16]. As a consequence, potential tissue injury depends on the balance between these two opposing pathways [10].

As abovementioned, SARS-CoV-2 enters human cells via ACE2 [8]. It has been shown that the expression of ACE2 would be reduced upon coronavirus infection [12]. Since RAAS is based upon a dynamic equilibrium between two opposite axes, the down-regulation of ACE2 leads to enhanced activity of the RAAS classical axis, which further promotes the internalization of ACE2 and results in a vicious circle of imbalance (Fig. 1) [10, 17]. We continue to discuss two hypotheses that explain how COVID-19 might affect serum potassium levels via ENaC.

Depleted potassium levels and ENaC hyperactivity

The over-activation of the ENaC plays a crucial role in urinary potassium loss and subsequently reduced serum potassium levels [18]. Interestingly, ENaC and ACE2 expression share similar distributions in the tissues, including renal tubules, urinary bladder, colon epithelium, lung airway, and alveoli [19, 20]. This channel modulates salt reabsorption and balances electrolyte homeostasis. ENaC activity is facilitated via a variety of factors, particularly aldosterone levels [20]. The over stimulation of the ACE/Ang II/AT1R axis, during the SARS-CoV-2 infection, may result in ENaC hyperactivity. Indeed, aldosterone, whose secretion is promoted by Ang II, binds to mineralocorticoid receptors and leads to the upregulation and enhanced activity of the ENaC [21]. Furthermore, Ang II has been shown to significantly improved ENaC activity via binding to AT1R [22]. ENaC function leads to increase in sodium reabsorption from luminal fluid, resulting in an accumulation of an intracellular positive charge [20]. Subsequently, the Na^+/K^+ ATPase pump on the basolateral border pumps intracellular sodium into the interstitium, in exchange for potassium. In turn, potassium exits the apical membrane through transport pathways, such as the renal outer medullary potassium (ROMK) channels and the Ca^{2+}-activated K^+ (BK) channels, causing kaluresis in the context of ENaC hyperactivity in the distal convoluted tubules [23].

Moreover, after the SARS-CoV-2 binds to the ACE2 receptor, the S protein is cleaved by host cell surface proteins, called type II transmembrane serine protease

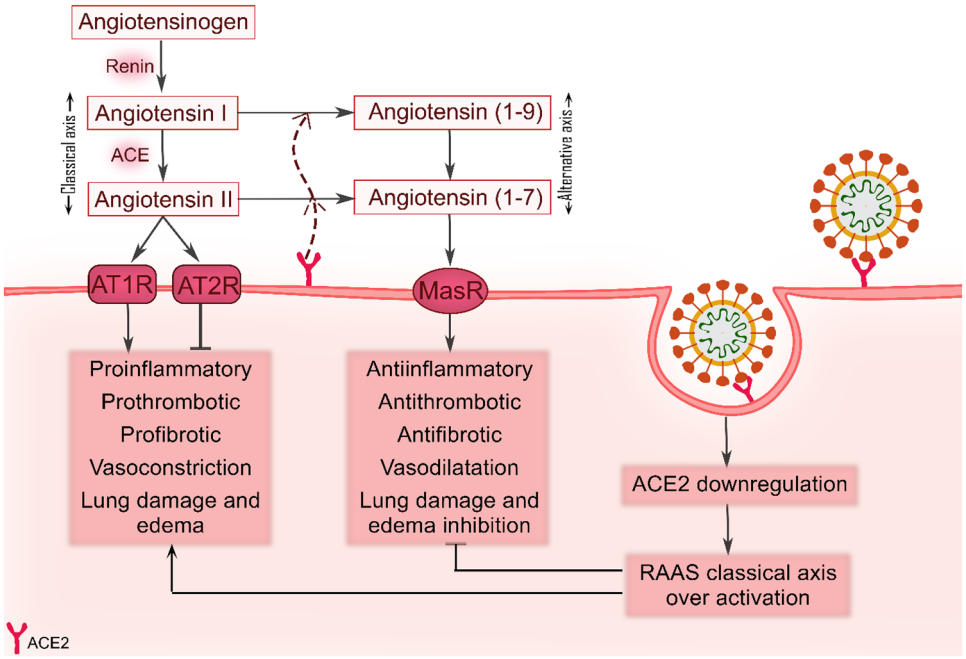

Fig. 1 Schematic of the possible role of RAAS in SARS-CoV-2 pathogenesis. Angiotensin I is generated through the action of renin on a precursor protein, Angiotensinogen. In the RAAS classical axis, ACE converts Angiotensin I to angiotensin II, leading to inflammation, thrombosis, fibrosis, vasoconstriction, and lung injury. Conversely, in the RAAS alternative axis, ACE2 inactivates Angiotensin II by producing Angiotensin (1–7), which induces biological activity distinct from Angiotensin II through binding with MasR. In the context of SARS-CoV-2 infection, the ACE-2 would be downregulated, thus mediating over activation of the RAAS classical axis. *RAAS* Renin angiotensin aldosterone system, *ACE* angiotensin-converting enzyme, *ACE2* angiotensin-converting enzyme 2, *MasR* mas receptor, *AT1R* angiotensin II type 1 receptor, *AT2R* angiotensin II type 2 receptor, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

(TMPRSS2), which facilitates viral fusion and cell entry [24]. TMPRSS2 expression is modulated by a guanine rich sequence which is capable of forming G-quadruplex structure in the promoter region of this gene [25]. Intracellular potassium ions can stabilize the G-quadruplex structure, hence down-regulating TMPRSS2 expression and impairing viral cell entry [25]. ENaC hyperactivity, due to ACE/Ang II/AT1R over stimulation results in intracellular loss of potassium, so leads to high expression of TMPRSS2 [18]. In an inhibitory feedback loop, TMPRSS2 can reduce ENaC activity, whereas in the case of COVID-19, ENaC remains activated without inhibition by TMPRSS2, because TMPRSS2 is utilized for viral cell entry mechanisms (Fig. 2, right panel) [18, 26].

To further support the importance of the previous hypothesis on the severity of COVID-19 infection, we discuss the role of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which is one of the main intracellular inflammatory pathways of the innate immune system [27]. An unrestricted immune reaction in SARS-CoV-2 pathogenesis, known as the "cytokine storm", leads to extensive tissue damage [28]. Interleukin (IL)-1β and IL-18 are two types of cytokines that are activated by NLRP3 [27]. In 2007, Pe´trilli et al. revealed that potassium efflux is the common and specific trigger of NLRP3 activation [29]. Therefore, potassium excretion, in the context of ENaC hyperactivity, may induce NLRP3 over activation, resulting in exacerbation of inflammatory responses and poor clinical outcomes [30–34]. Ultimately, according to this hypothesis, ENaC over stimulation, due to viral-mediated ACE2 downregulation, induces the loss of potassium from epithelial cells, which may cause low serum potassium concentration.

Elevated potassium levels and ENaC hypoactivity

The second hypothesis describes the role of furin, a type of proprotein protease, which is an important reason for the higher infectivity of SARS-CoV-2, compared with other coronaviruses [35, 36]. Furin facilitates the binding of the virus to ACE2 by cleaving its Spike protein [37]. In addition, furin is necessary for activating the ENaC by cleaving its α-subunit at two cleavage sites [38]. Recent research has shown that the furin cleavage site of the SARS-CoV-2 spike protein is identical to the furin-cleavable peptide sequence on the ENaC α-subunit [39]. Indeed, furin is essential to the activity and expression of ENaC, but in this instance, it is hijacked by SARS-CoV-2, creating competition for furin use following infection with the virus [40]. Without

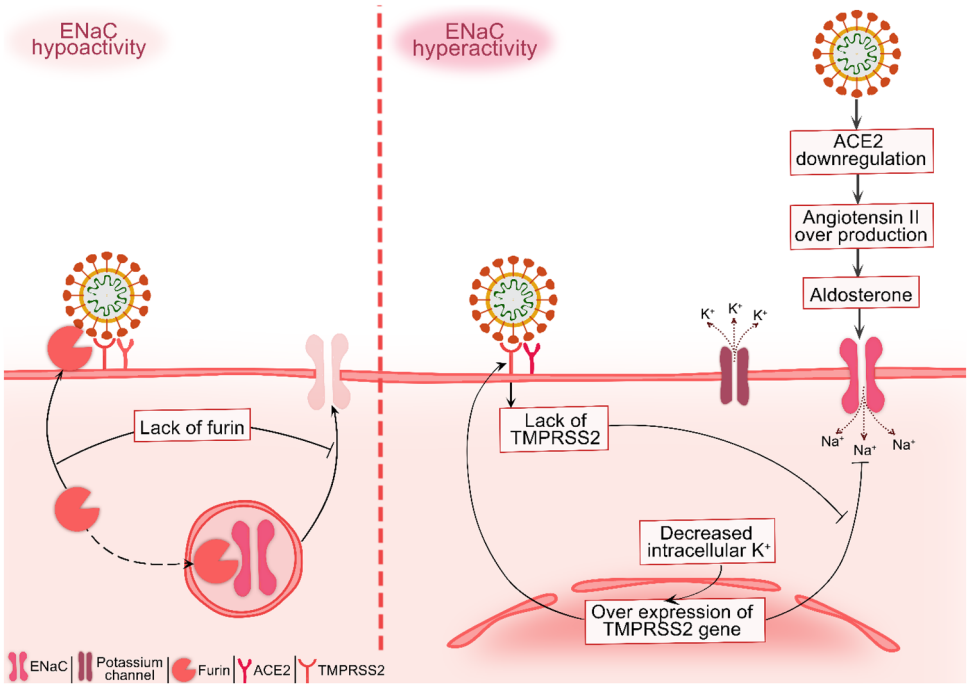

Fig. 2 Schematic of the hypothetical impact of SARS-CoV-2 infection on ENaC. Over activation of the RAAS classical axis leads to the stimulation of aldosterone secretion. Aldosterone enhances the activity of ENaC in the apical cell membrane, which results in the excretion of potassium out of the cell and into the luminal space. Decreased intracellular potassium induces the TMPRSS2 gene to be over expressed. TMPRSS2 is capable of inhibiting ENaC activity, which would be utilized by SARS-CoV-2 and so ENaC remains activated (right panel). SARS-CoV-2 spike protein harbors a furin cleavage site which is similar to the ENaC furin-cleavable peptide. Furin is hijacked by SARS-CoV-2, meaning the ENaC cannot be assembled and become hypoactivated (left panel). *RAAS* Renin angiotensin aldosterone system, *ENaC* epithelial sodium channel, *ACE2* angiotensin-converting enzyme 2, *TMPRSS2* type II transmembrane serine protease, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

furin-mediated cleavage, a decreased in the efficacy of ENaC is likely (Fig. 2, left panel). This may have a negative effect on epithelial cells and disturb the water or electrolyte homeostasis, leading to elevated serum potassium levels. ENaC dysfunction may be better understood by studying its genetic disorders. Pseudohypoaldosteronism is a condition in which ENaC subunits undergo a loss of function mutation, typically manifested by hyperkalemia, metabolic acidosis, and hypertension [41]. Furthermore, ENaC plays a critical role in lung fluid clearance, meaning that reduced ENaC activity may explain why patients with COVID-19 sometimes die of severe pulmonary edema [40, 42].

Interaction between emerging SARS-CoV-2 therapeutic agents and ENaC activity

In recent months, several promising therapeutic approaches have been developed [43]. While membrane-bound ACE2 facilitates SARS-CoV-2 cell entry, a modified form of soluble ACE2, called human recombinant soluble ACE2 (hrsACE2), could competitively bind to the virus, which should theoretically be beneficial in the treatment of COVID-19 [44]. Indeed, binding hrsACE2 to the spike protein may mediate SARS-CoV-2 neutralization and rescue cellular ACE2 activity, which have been linked to protecting multiple organs from injury by reducing Ang II levels [45]. As the RAAS equilibrium shifts to the alternative axis, normalization of ENaC activity would be feasible. In addition to hrsACE2, protease inhibitors capable of reducing TMPRSS2 activity are among the novel therapeutics under development [46]. Camostat mesilate, a TMPRSS2 blocker, has been shown to inhibit SARS-CoV-2 infection [47]. In addition to its antiviral activity, Camostat mesilate is well-known for its anti-hypertensive properties and renoprotective effects, since it reduces the activity of plasmin which cooperates with furin in cleaving and subsequently activating the ENaC [48–50]. Considering the inhibitory impact of TMPRSS2 on ENaC, camostat mesilate would be able to enhance ENaC activity by blocking TMPRSS2, but blocking of plasmin activity may impair the ENaC activity. Therefore, this paradoxical issue will be resolved through further investigations measuring the net effect of camostat mesilate on ENaC activity in the context of SARS-CoV-2 infection. Bromhexine, a potential therapeutic option, is another blocker of TMPRSS2 enzyme with ENaC blocking

effects [51]. Finally, furin is a potential therapeutic target for COVID-19 and furin inhibitors are assumed to reduce ENaC assembly and impair electrolyte balance [52, 53]. In summary, whatever new therapy emerges for treating COVID-19, dealing with the disruption to the patients' electrolyte homeostasis is vital.

Conclusion

SARS-CoV-2 can lead to both decreases and increases in serum potassium levels. As previously mentioned, the prevalence of hypokalemia is higher in patients with COVID-19, so it seems that the first hypothesis has a stronger impact on potassium abnormalities, and since most patients show mild degrees of potassium depletion, the second hypothesis might act as a mitigator of the first. Further molecular investigations are warranted in order to clarify the exact role of ENaC in SARS-CoV-2 pathogenesis.

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Declarations

Conflict of interest The authors declare that there is no conflict of interests.

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