




Calcium sensing receptor hyperactivation through viral envelope protein E of SARS CoV2: A novel target for cardio-renal damage in COVID-19 infection

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Abstract

Over the recent decades, a number of new pathogens have emerged within specific and diverse populations across the globe, namely, the Nipah virus, the Ebola virus, the Zika virus, and coronaviruses (CoVs) to name a few. Recently, a new form of coronavirus was identified in the city of Wuhan, China. Interestingly, the genomic architecture of the virus did not match with any of the existing genomic sequencing data of previously sequenced CoVs. This had led scientists to confirm the emergence of a new CoV strain. Originally, named as 2019-nCoV, the strain is now called as SARS-CoV-2. High serum levels of proinflammatory mediators, namely, interleukin-12 (IL-12), IL-1 β , IL-6, interferon-gamma (IFN γ), chemoattractant protein-1, and IFN-inducible protein, have been repeatedly observed in subjects who were infected with this virus. In addition, the virus demonstrated strong coagulation activation properties, leading to further the understanding on the SARS-CoV2. To our understanding, these findings are unique to the published literature. Numerous studies have reported anomalies, namely, decline in the number of lymphocytes, platelets and albumins; and a rise in neutrophil count, aspartate transaminase,

alanine aminotransaminase, lactate dehydrogenase, troponins, creatinine, complete bilirubin, D-dimers, and procalcitonin. Supplementation of calcium during the SARS CoV-2 associated hyperactive stage of calcium-sensing receptors (CaSR) may be harmful to the cardio-renal system. Thus, pharmacological inhibition of CaSR may prevent the increase in the levels of intracellular calcium, oxidative, inflammatory stress, and cardio-renal cellular apoptosis induced by high cytokines level in COVID-19 infection.

KEYWORDS

COVID-19 infection, SARS CoV-2, Calcium Sensing Receptor, CRP, Neutrophils, Myeloperoxidase

1 | INTRODUCTION

COVID-19 is a deadly viral illness which may lead to the development of severe respiratory distress. On 11 March 2020, the WHO declared the epidemic a global pandemic, as COVID-19 spread rapidly across the globe (Singh, Gupta, Satija, Pabreja, et al., 2020). In a major reported survey, 15.7% of COVID-19 patients undergoing hospitalization experienced serious illness, 5% have been admitted to ICU, 2.3% required intubation and 1.4% of the subjects eventually died due to multiple organ failure (Baud et al., 2020; Wang, Du, et al., 2020). Cardiovascular risks, such as, acute myocardial injury (12%) (Yang et al., 2020), heart failure (Azevedo et al., 2020), and arrhythmias (44%) (Wang, Hu, et al., 2020), have been recorded in recent SARS-CoV2 infections. Further, in a study, 12% of COVID-19 patients who did not have a history of CVDs reported elevated troponin levels that led to cardiac arrest during the time of hospitalization (Zheng et al., 2020). According to the reports from hospitalized patients, the prevalence of acute kidney injury for serious cases was 29%, whereas, it was 69.57% in the 60 year old age category and above (Diao et al., 2020).

Due to elevated serum proinflammatory mediators, such as, IL-1 β , IL-6, IL-12, MCP-1, IFN γ , and IFN-inducible protein, the SARS-CoV2 is correlated with coagulation activation (Huang et al., 2020). As far as we know, these findings are specific to published literature. Several studies have documented abnormalities in COVID-19 laboratory experiments, namely, decline in the number of lymphocytes, decline in the number of platelets, and declined albumin levels. In addition, there was an abnormal rise in neutrophil count, D-dimers, AST, ALT, LDH, troponins, complete bilirubin, creatinine, prothrombin time (PT), procalcitonin and C-reactive protein (CRP). Calcium shifts were not yet observed. However, there were data of patients that suggested a drop in overall serum calcium (TCa, mmol/L) and real ionizing total blood calcium (Ca $^{2+}$, mmol/L). We also analyzed blood pH levels from various studies to assess the probability of raised pH in COVID-19 patients as a consequence of hyperventilation which could induce Ca $^{2+}$ reductions (Cappellini et al., 2020). The calcium ion not only functions as an intracellular signaling molecule but also associates the stimulation of extracellular receptors to intracellular events. However, a drop in the serum calcium levels during COVID-19 is known to be a significant event, which involve the activation of different nucleases, proteases, and, indirectly, the production of cytokines, prostaglandins,

and superoxide radicals that could cause cell damage and death (Cappellini et al., 2020; Zaloga, 1992).

1.1 | Selection of literature for review

Technically relevant findings were gathered from Medline/Mendeley/ ScienceDirect/Google Scholar/PubMed and Springer link databases. Several keywords were used in the literature search, alone and in combination. Some of the keywords employed were, "COVID-19 infection," "Epidemiology of Cardiac and renal pathology in COVID-19 infection," "Pathophysiology of SARS-CoV-2," "Involvement of viral envelop protein E of SARS-CoV-2," "Mechanism of Calcium Sensing Receptor," and "Hyperactivated state of Calcium Sensing Receptor-mediated cardio-renal cell injury." The present paper considered journal articles that were written only in English language. Moreover, reference lists of the sources were screened to search for related journal content that were not found during the initial search.

1.2 | Role of SARS CoV-2 envelop protein E during COVID-19 infection

SARS-CoV-2 is a type of Beta-CoV that is composed of the viral lineage B. Taxonomically, this strain is closely related to coronaviruses transmitted by bats, with a total identity of 96% (Singh, Gupta, Mishra, Chellappan, & Dua, 2020). The virus is now reported to infect host cells through a mechanism where it interacts with TMPRSS2, the serine protease and ACE2 receptors that are located largely on the plasma membranes of the epithelial cells found in the respiratory tract and the upper esophagus (Hoffmann et al., 2020). Singh et al., have demonstrated that, this virus often infects many other cell forms, including, epithelial stratified cells, colonic cells, enterocytes that are absorbent in function, specialized cells such as cholangiocytes, proximal tubular cells of the nephron, renal cells, and myocardial cells (Singh, Gupta, Satija, Negi, et al., 2020). GenBank entries of 1 β alpha, beta, and gamma CoV genomic sequences extracted with Open Reading Frames (ORFs) demonstrate that Ca $^{2+}$ is vital to the growth, entry, gene-expression, maturation, and for the release of viruses during viral infections (Zhou et al., 2009). The coronaviral genome is encoded with the spike (S) protein, nuclear protein (N), membrane (M), and

envelope (E) proteins, all of which are sufficient to generate the structurally complete viral particle of the coronavirus. In vivo and in vitro models of SARS-CoV infection have shown that, the SARS-CoV E gene encodes a small ion channel-participation transmembrane protein, which is synthesized profusely during infection. This is located predominantly in the intermediate ERGIC and Golgi apparatus. These channels are Ca²⁺-permeable that alter calcium homeostasis in the cell and have been shown to facilitate activation of inflammatory pathways leading to increased levels of TNF- α , IL-6 and IL-1 β , that are associated with cardio-renal cell injury (Gabarre et al., 2020; Lubrano & Balzan, 2020; Nieto-Torres et al., 2014; Nieto-Torres et al., 2015).

Physiologically, the cargo proteins synthesized by ER must be dissociated from their ERGIC receptors for effective anterograde transmission from the ERGIC to the Golgi. The cell acidification studies performed in cultures reveal inhibition of ERGIC-53's interaction with its transported procathepsin Z. It is also understood that, the neutralization of organelle pH with chloroquine directly impairs its dissociation into the ERGIC (Appenzeller-Herzog et al., 2004). It is well known that calcium is required to bind ERGIC-53 to its substrates (Appenzeller et al., 1999; Itin et al., 1996). A mechanism that maintains lower ERGIC calcium levels

would therefore be able to facilitate the release of pH-induced transport of protein substrates. Imaging of total calcium in fast-frozen, freeze-dried PC12 cells (i.e. the volume of free and bound calcium) has shown high calcium concentrations in ER and Golgi. However, calcium was not detected in ERGIC components (Pezzati et al., 1997). This route is different from the traditional ERAD route, which essentially focusses on ER preservation of misfolded proteins. The shifts in free calcium and pH from the ER to the ERGIC may be a crucial factor, which warrants thorough investigation during the SARS CoV-2 infection (Figure 1).

1.3 | Pathophysiology of viral envelop protein E of SARS CoV-2 associated hyperactivation of CaSR-mediated cardio-renal cell injury

The extracellular CaSR is a superfamily member of GPCRs observed to be expressed in the heart, kidney, parathyroid, and various other tissues including the gastrointestinal tract and immune cells that participate in systemic calcium homeostasis modulation. Its primary physiological role is to detect minor shifts in extracellular Ca²⁺,

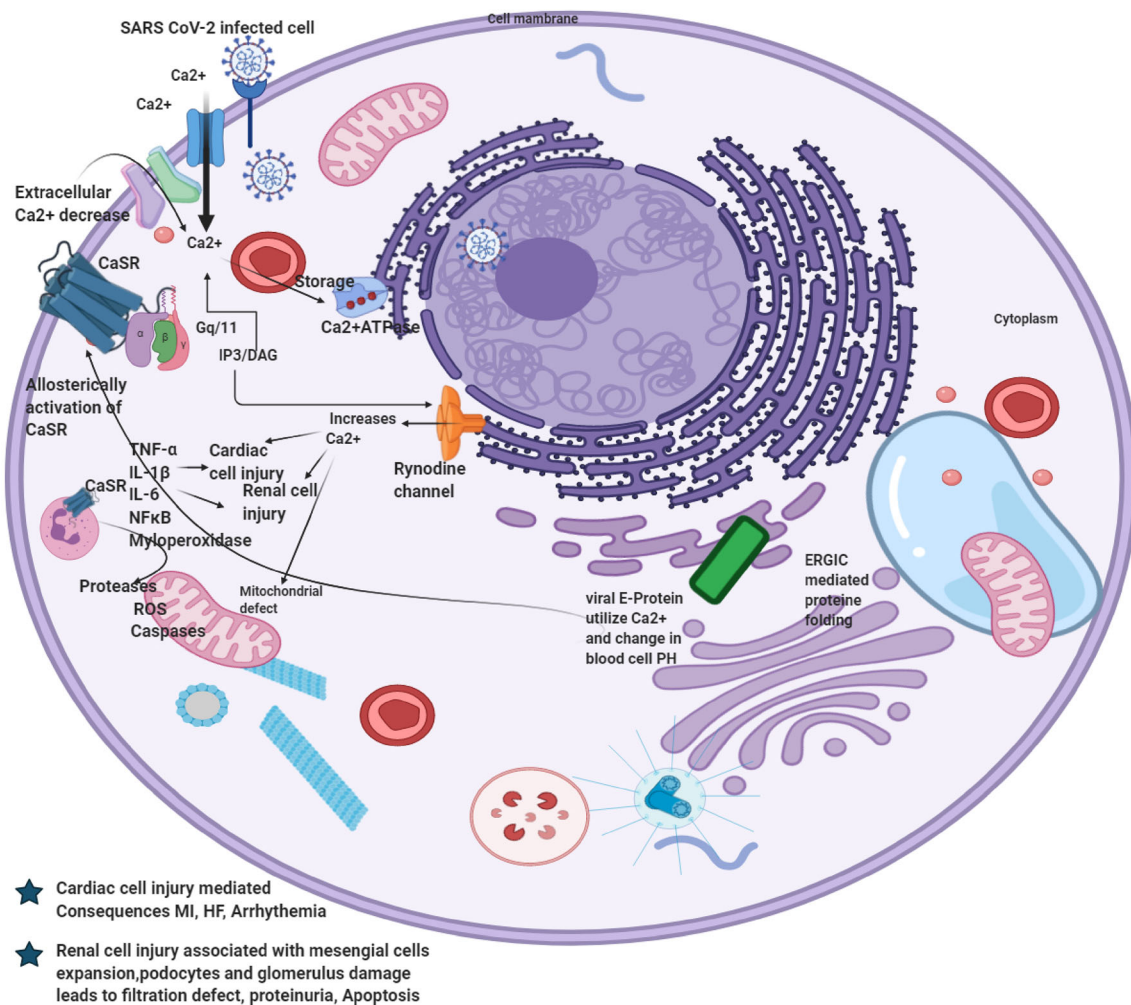


FIGURE 1 Exploration of calcium sensing receptor (CaSR) hyper activation through viral envelop protein E of SARS CoV2 mediated cardio-renal cell damage in COVID-19 infection

modulating the PTH release and maintaining a steady concentration of Ca²⁺ in blood. A recent study has reported that, CaSR activation may result in intracellular calcium release through G-PLC-IP₃ pathways. In addition to CaSR's function in the management of parathyroid secretion and reabsorption of calcium from the kidneys, there are several other evidences that suggest the importance of CaSR activation in the progression of a range of different cardio-renal disorders. During COVID-19 infection, serum calcium dyshomeostasis arises due to enhanced calcium utilization by SARS CoV-2 envelope E protein which leads to a change in extracellular calcium concentration. Furthermore, extracellular Ca²⁺, CaSR may also be activated by different stimuli such as, ionic strength, polyamines, polyvalent cations, l-aromatic amino acids, and pH (Riccardi et al., 2009; Saidak et al., 2009). CaSR has been shown to stimulate various downstream cellular signaling pathways in response to extracellular Ca²⁺ bindings, including, Gq-coupled phosphatidylinositol phospholipase C stimulation, Gi-coupled inhibition of adenylyl cyclase, and multiple protein kinases activation, including extracellular signal-reliant kinase 1/2 (ERK1/2) and phosphatidylinositol 3-kinase (PP) (AKT). Cellular pH transition changes in COVID-19 infection triggers the CaSR, leading to G-protein-dependent activation by Gq/11 from PLC action. This in turn triggers IP₃ and rapid intracellular ion release (Ca⁺⁺)₁ followed by extracellular ions of calcium (Ca⁺⁺)₀ (Thakker, 2012) through the opening of various channels including TRPC and L-type calcium channels in cardiac tissues. Thus, the triggered calcium is now sensed via sarcoplasmic endoplasmic reticulum calcium ATPase (SERCA) and stored in the sarcoplasmic endoplasmic reticulum (SER). The SER concentration of calcium increases at each contraction of the myocardium, which produces a heavy release of calcium via a ryanodine-1 channel. In addition, there are reported evidences suggesting the presence of CaSR on immune cell surfaces, including, neutrophils and T lymphocytes. CaSR activation in isolated neutrophils has resulted in enhanced secretion and overexpression of the pro-inflammatory protein, NFκB and the enzyme, myeloperoxidase (Zhai et al., 2017). T lymphocyte CaSR expression in COVID-19 causes apoptosis, TNF-α stimulation, and IL-4 cytokine production (Wu et al., 2015). These results indicate that CaSR may contribute to neutrophil activation, repression of T cells, and inflammatory cytokine release, contributing to cardiomyocyte damage and myocardial consequences in COVID-19 infection.

On the other hand, in the renal system, calcium ion is a well-known regulator of the activity of podocytes under physiological and pathological circumstances. Podocytes are specific cells that form filtration splits between glomerular filtration barrier foot systems, thereby preventing leakage of proteins into urine. The rise in podocyte-calcium influx triggers a contractile phenotype in podocytes and could weaken the dynamics of the podocyte cytoskeleton (Faul et al., 2008). Furthermore, in vitro studies have shown the overuse of CaSR activator induced calcium influx in podocytes by TRPC-6 (Zhang et al., 2017). It is therefore rational to assume that calcium imbalance mediated harm to podocytes may attribute to the activation of CaSR, which may lead to mesangial expansion, proteinuria, apoptosis, and glomerular injury (Kwak et al., 2005).

2 | CONCLUSION

We conclude that, the supplementation of calcium during SARS CoV-2 associated hyperactive stage of CaSR may harm the cardio-renal system. Furthermore, inhibition of CaSR may also regulate increased levels of intracellular calcium, oxidative stress, pro-inflammatory mechanisms, and cardio-renal cellular apoptosis, which are adversely induced by high cytokine levels in COVID-19 infection.

CONFLICT OF INTEREST

The authors state that the study was undertaken without any commercial or financial arrangements that might be interpreted as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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