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Viewpoint

SARS-CoV-2, Hypoxia, and Calcium Signaling: The Consequences and Therapeutic Options

Chhanda Charan Danta*

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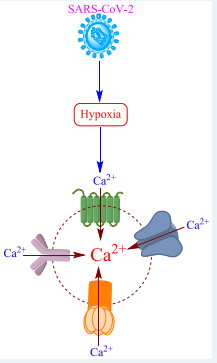
ABSTRACT: Currently, COVID-19 has created difficulties in understanding the pathological mechanisms and therapeutic options for treatment. COVID-19 patients have shown to be hypoxic, and hypoxia causes alteration of the cell calcium dynamics, which leads to alterations in many signal transduction pathways and gene expression. Also, both viruses and hypoxia directly alter many pathological and biochemical pathways, such as inflammation, cytokine signaling, glycolysis, and calcium signaling. Therefore, understanding of these cellular events would be useful in finding therapeutic options.



KEYWORDS: *SARS-CoV-2, COVID-19, hypoxia, calcium signaling, inflammation, therapeutics*

Human cells need a constant supply of oxygen for their survival, energy production, and normal function. However, hypoxia may lead to cell death. Therefore, many cellular mechanisms have been predicted of how cells adapt and behave in hypoxic conditions, which have been investigated through oxygen-sensing cells that how changes in the oxygen tension transduce signals into different organ systems and their functions. The hypoxic response is very complex as it regulates many signal transduction pathways and expression of genes. Recently, it has been reported that the novel SARS-CoV-2 causes hypoxia,[1] and earlier investigation has supported that hypoxia leads to alteration in Ca^{2+} cell signaling.[2] During hypoxia, an increase in intracellular Ca^{2+} concentration has been observed in many cells.[3,4] Furthermore, the pathophysiological correlation between hypoxia signaling and inflammation are bidirectional. Hypoxia could activate the cytokine storm and inflammatory pathways and affect the fate of immune cells and functions.[1] Recently, it has been reported that the severity and death of COVID-19 patients is due to the hyperinflammation and activation of cytokine signaling.[5] Therefore, understanding these molecular mechanisms would be highly useful in prescribing or designing therapeutic approaches for the treatment of COVID-19 during the present global pandemic situation. The clinical symptoms of COVID-19 infected patients have been evidenced that the novel SARS-CoV-2 is responsible for causing hypoxia and respiratory distress. Earlier, it has been well established that a virus infection can trigger a metabolic shift and can activate the glycolytic process which leads to hypoxia and inflammation. Recently, it has been reported that the loss of lung perfusion regulation, low oxygen vasoconstriction, and increase of coagulopathy are the major mechanisms of hypoxia in COVID-19.[6] The critical hypoxic state observed in COVID-19 patients is due to the small increase in partial arterial pressure of oxygen, even though the increase amount of inspired oxygen fraction delivered has been significantly noted during conventional oxygen supplementation.[7] Additionally, many viruses replicate efficiently under hypoxia.[8] Viruses also reprogram the host cellular function, which is an essential strategy for their replication, maturation, and survival, including hijacking the calcium channels and pumps and increasing the intracellular Ca^{2+} load.[9]

SARS-CoV-2 has been reported to activate the hypoxia-inducible factor (HIF-1) pathway.[1] Therefore, it can induce many downstream processes such as alteration of host cellular metabolism, acceleration of inflammation, and facilitation of rapid viral replication. In a hypoxic state, cells generally regulate the expression of genes, mostly those involved in glycolysis and metabolism of iron and in the control of angiogenesis for adaptation and survival. HIF-1 is the transcriptional activator of several genes concerning cellular adaption in the hypoxic state.[1]

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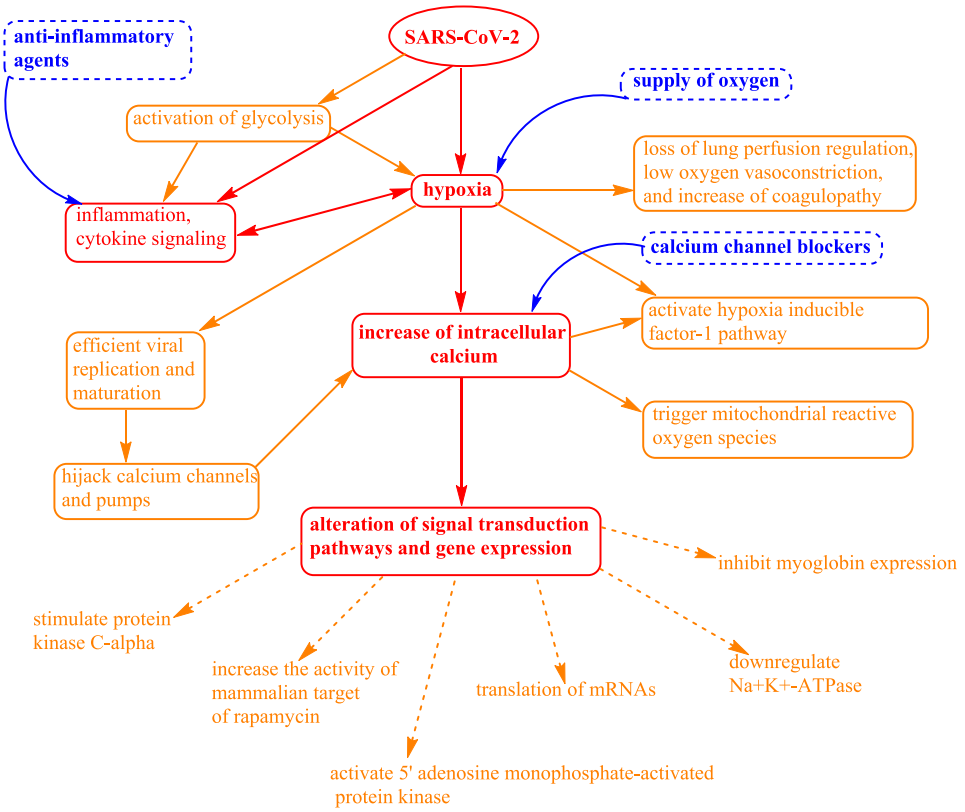

Figure 1. Cellular events due to SARS-CoV-2, hypoxia, inflammation, and Ca^{2+} signaling and the therapeutic options.

HIF-1α can increase the expression of glycolytic genes through binding hypoxia-responsive elements of glycolytic promoter genes.[8]

Furthermore, lactic acid is another viral-induced glycolytic product which reduces blood pH and causes respiratory acidosis and hypercapnia. Recently, an increase in lactate dehydrogenase (LDH) has been observed in severe COVID-19 patients.[10] It is important to emphasize that increased LDH levels have been associated with severe disease conditions and an increased mortality rate of COVID-19 patients.[10] Furthermore, LDH converts pyruvic acid to lactic acid during low oxygen environment. LDH has also been a marker of cardiac damage, therefore, its abnormal values may be due to multiple organ injury and may also be due to hypoxia and upregulation of the glycolytic pathway. The critical respiratory conditions in COVID-19 patients may be due to the increase of LDH levels.

Besides, hypoxia also leads to alteration of Ca^{2+} signaling in cells. The experimental investigation suggested that hypoxia could increase the intracellular Ca^{2+} concentration in pulmonary arterial myocytes through triggering mitochondrial reactive oxygen species (ROS).[4] ROS are the high energetic free radical species which can cause damage to macro-biomolecules, such as nucleic acids, proteins, lipids, and carbohydrates, and ultimately lead to apoptotic cell death.[11] Through an *in vitro* study, it has been analyzed that chronic hypoxia altered the Ca^{2+} signaling in airway smooth muscle cells, which led to an increase in airway responsiveness.[12] Furthermore, it has been reported that hypoxia can stimulate translation of HIF-1α and HIF-2α through the distribution of HIF-α mRNAs to a larger fraction of polysomes. This process needs extracellular Ca^{2+} entry, stimulation of protein kinase Cα (cPKCα), and the activity of mammalian target of rapamycin (mTOR). This experiment has established an important physiological mechanism that hypoxia stimulates extracellular Ca^{2+} entry selectively, which induces the translation of mRNAs that required adaptation under hypoxia conditions.[13] Working with rats' hippocampal neurons, it was concluded that both types of high voltage-activated (HVA) Ca^{2+} channels such as N-type and L-type were sensitive in hypoxia conditions. Also, the L-type Ca^{2+} channel was found to be more sensitive to a low oxygen environment.[14] Furthermore, experimental data suggested that in hypoxia, Ca^{2+} influx via Ca^{2+} release-activated Ca^{2+} (CRAC) channels led to $Na^{+}K^{+}$-ATPase downregulation, 5′ adenosine monophosphate-activated protein kinase (AMPK) activation, and alveolar epithelial dysfunction.[2] To understand the role of Ca^{2+} in signal transduction pathways which regulate gene expression, dopaminergic pheochromocytoma (PC12) on the oxygen sensing cell line has been used in hypoxic conditions. The results showed an immediate response from PC12 cells causing membrane depolarization and an increase of the intracellular Ca^{2+} concentration in hypoxia. It was concluded that the increase of intracellular Ca^{2+} led to cell injury and death due to hypoxia.[3] Hypoxia can also be responsible for the inhibition of myoglobin expression through the alteration of Ca^{2+} entry in response to cell depolarization or by the depletion of Ca^{2+} storage from the endoplasmic reticulum.[15] The cellular events due to SARS-CoV-2, hypoxia, inflammation, and Ca^{2+} signaling along with the therapeutic options have been summarized in Figure 1.

Therefore, clinical investigation on the application of oxygen, anti-inflammatory agents, and calcium channel blockers for the treatment of COVID-19 patients could be very useful.

AUTHOR INFORMATION

Corresponding Author

Chhanda Charan Danta − *Centre for Atherothrombosis and Metabolic Disease, Hull York Medical School, University of*

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Hull, Hull HU6 7RX, United Kingdom; orcid.org/0000-0002-1436-9461; Email: ccdanta2011@rediffmail.com

Complete contact information is available at: https://pubs.acs.org/10.1021/acsptsci.0c00219

Notes

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