sciendo

J Biomed Clin Res Volume 15 Number 2, 2022

DOI:10.2478/jbcr-2022-0015

Review

COVID-19: SOME PATHOPHYSIOLOGICAL AND ENDOCRINE ASPECTS

Katya N.Todorova

Clinic of Endocrinology and Diseases of Metabolism,
Dr. G. Stranski University Hospital, Pleven
Medical University – Pleven

Summary

The pandemic caused by COVID-19 infection almost two years ago is associated with many unknown multi-organ damages, including the endocrine system. Based on the fact that endocrine gland tissues express ACE-2 and TMPRSS2, it has been suggested that they may be directly attacked by the virus and cause toxic effects on them directly or indirectly by an autoimmune mechanism. Hypothalamic-pituitary-adrenal axis hormones are crucial for the course and progression of the disease and modulate the magnitude of the immune response and adaptation to stress. The aim of the present review is to summarize the state of the art in the COVID-19 and endocrine problems in its clinical and pathophysiological part and to answer the question of to what extent patients with COVID-19 have a higher risk of adverse outcomes.

Keywords: SARS-CoV-2, COVID-19, ACE-2, hypothalamic-pituitary-adrenal hormonal axis

Introduction

In December 2019, a new, previously unknown virus belonging to the Corona class of viruses was identified that caused atypical pneumonia and acute respiratory distress syndrome and led to the deaths of thousands of people in China's Hubei Province, with Wuhan as the capital. The isolated virus was named Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 for short, and the disease COVID -19.

The rapid and widespread spread of the disease that occurred gave the WHO the reason to declare COVID-19 infection a global pandemic [1]. To address the pandemic, health systems in all countries had to be reorganized to ensure that all those in need had access to adequate medical care.

SARS-CoV-2 is the third described high-risk coronavirus after the other two coronaviruses already known to have caused the two previous outbreaks: the first of Severe Acute Respiratory Syndrome [SARS] in 2002-2003, caused by SARS-CoV-1, which occurred in southern

Corresponding Author:
Katya N. Todorova
Clinic of Endocrinology and Metabolic Diseases,
Dr. G. Stranski University Hospital,
Second Clinical Base
91, Vladimir Vasov Str.
Pleven 5800,
Bulgaria
e-mail: todorova_kate@abv.bg

Received: March 10, 2022
Revision received: May 5, 2022
Accepted: August 5, 2022

China, and the second Middle East respiratory syndrome (MERS), caused by a similar coronavirus, MERS-CoV, first isolated in Saudi Arabia in 2012 [2]. Although there have been no reported cases of SARS worldwide since 2004, following the containment of the outbreak caused by SARS-CoV-1, it is striking that the related virus SARS-CoV-2, which caused the current global pandemic, has again been isolated from China [3].

Morphological characterization of coronaviruses

The causative agent of COVID -19, SARS-CoV-2, is a highly transmissible and highly pathogenic novel type of coronavirus that continues to be a threat to human and public health. There is a high degree of similarity between it and the other two coronaviruses, SARS-CoV-1 and MERS-CoV. They all possess a genome that is made up of one long, repeatedly coiled-coiled single-stranded RNA. These genomes are characterized by a high mutation rate[4].

It has been shown that, due to genome-wide nucleotide sequence, similarities exist in the phylogeny-based pathogenicity of the two SARS viruses[5]. The genomic characterization of SARS-CoV-2 and SARS-CoV-1 shows 80% nucleotide base identity, while it is 50% between SARS-CoV-2 and MERS-CoV [6]. A similar similarity was observed concerning the primary protein structure of the two SARS-Co viruses, which reached 95% homology in the amino acid sequence of the major proteins. This biological similarity between SARS coronaviruses explains the non-significant differences in terms of their infectivity, transmissibility, cell invasion, tissue distribution, pathophysiological disorders, clinical activity, and variability [7]. All coronaviruses contain four structural proteins: spike [S], nucleocapsid [N], envelope [E], and membrane [M]. The spike (spike) S protein is responsible for the attachment of the virus to its receptor and entry into the cellular environment. The nucleocapsid is required for the formation of ribonucleoproteins. The packaging protein "packages" viruses in a concentrated form and maintains their ability to pass through the ion channels of the cell membrane. M protein is involved in the aggregation of new virus particles.

The affinity of the S protein for its membrane receptor is essential for the entry of coronaviruses into the cell. The spike protein consists of two functional subunits, of which the S1 subunit is of greater importance. Uncoupling of the S protein's ligand activity begins after binding to two host cell proteases that translocate the receptor contact sites of the spike protein from an inactive to an active position in subunit S1.

The mechanism of viral invasion is common to SARS-CoV-1 and SARS-CoV-2. This mechanism is mediated by the binding of the virus to the angiotensin-converting enzyme-2(ACE2) protein, which acts as its receptor. Also involved are the transmembrane serine protease TMPRSS2 and, to a lesser extent, cathepsin B, a cysteine protease [8]. The already internalized virion is replicated in infected cells, thus maintaining its life cycle. The process of viral entry into the cells is denoted as a lysosomal activated cellular pathway. M glycoprotein is required to overcome the lipid cell-membrane barrier, which, together with S protein, contributes to the stronger binding of the virus to the host cell membrane receptors.

Unlike SARS-CoV, the other type of coronavirus - MERS-CoV, uses the enzyme dipeptidyl peptidase-4 (DPP4) as a receptor for transmembrane passage [9]. After the binding of MERS-CoV to the DPP-4 binding domain, rapid virus internalization occurs, followed by virus replication. Characteristic of MERS-Co-V is its affinity for T lymphocyte cells and its interaction with nuclear factors, such as nuclear factor kappa b (NF-kB), which is a key factor in the pathogenesis of inflammatory diseases [10].

Virus-receptor modulation and significance of Renin Angiotensin-Aldosterone System

The common receptor of the two coronaviruses, SARS, is angiotensin-converting enzyme-2, which is a transmembrane zinc-dependent mono carboxypeptidase and a key player in the renin-angiotensin-aldosterone system (RAAS). ACE2 is expressed in various human tissues, predominantly in kidney, adrenal, adipose tissue, thyroid, vascular endothelium, pancreas, testis, ovary, and pituitary [11].

There is structural homology between ACE2

and angiotensin converting enzyme (ACE). Both are key enzymes of the RAAS but act on different substrates. Under physiological conditions, ACE converts angiotensin I (Ang I) to angiotensin II (Ang II), and ACE2 converts Ang I to angiotensin 1-9 and cleaves Ang II to angiotensin 1-7 [Ang-(1-7)]. These two processes proceed simultaneously, and the synthesized end products Ang II and Ang-(1-7) are in equimolar concentrations.

Both substrates must bind to their receptors to exert their biological action. Under physiological conditions, Ang II binds to its first receptor, angiotensin receptor 2 (AT 2), to which it has a strong affinity. Under nonphysiological conditions or when synthesized in supraphysiological concentrations, it also binds to its second alternative receptor, angiotensin receptor 1 (AT 1), to which it usually has a weak affinity. Ang II has potent vasopressor and hypertensive effects.

The Ang-(1-7) binding receptor is called Mas and is a G protein-coupled receptor. The resulting Ang-(1-7)/Mas ligand complex influences RAAS activity negatively [12]. Ang-(1-7), unlike Ang II, acts as a vasodilator and endothelial protector, reducing blood pressure by stimulating nitric oxide synthase [13]. By antagonizing Ang II's action, Ang-(1-7) reduces fasting glycemia, improves glucose tolerance, prevents pancreatic β-cell apoptosis, stimulates pancreatic β-cell proliferation, reduces thrombus formation, and improves renal function.

Depletion of ACE2, due to its binding to SARS-CoV-2, blocks Ang-(1-7) formation. Ang-(1-7) synthesized in minute amounts is insufficient to bind to and activate the Mas receptor and cannot oppose the action of Ang II [14]. The balance between ACE/ACE2 and Ang II/Ang-(1-7) is disturbed in favour of ACE and Ang II, and the clinical effects of Ang II become predominant. Ang II produced in abnormally high amounts depletes the binding capacity to AT type 2 receptors and begins to occupy AT type 1 receptors, thereby multiplying the potency and duration of its action [15]. A constant continuum is maintained due to the imbalance in concentrations between ACE/ACE2, in which ACE predominates. It has a detrimental effect on the clinical evolution of various diseases, such as diabetes, hypertension, myocardiopathy, nephropathy, and also on the prognosis of patients with Covid-19 because Ang II can stimulate cell growth, fibrosis, epithelial cell apoptosis, generation of reactive oxygen radicals and release of proinflammatory cytokines, thereby enhancing the deleterious effect of infection.

Virus-associated depletion of ACE2 also exerts another adverse effect on the protein collectin. Collectin is a homologue of ACE2, and under physiological conditions, they are synergized in their biological action. They positively affect innate immunity, the coagulation cascade, and amino acid transport in enterocytes and renal nephrons. At low levels of ACE2, collectin cannot realize its action, and aminoaciduria, suppression of immune responses, hypertension, and hypercoagulability occur [16].

A comparison of the pathological characteristics of the two SARS-CoV viruses shows that the binding fineness of SARS-CoV-2 to the ACE2 binding domain is about 20-30 times higher than that of SARS-CoV-1 to ACE2. This difference in precision explains the dramatically higher transmembrane intracellular permeability for SARS-CoV-2 on the one hand, and the more pronounced vasopressor activity, endothelial injury, thrombus formation, and fibrosis, on the other [17].

Covid-19 and endocrine-pathophysiological and clinical characteristics

As early as 2003, SARS-CoV-1 was found to have an extrapulmonary manifestation, causing concomitant acute-onset polyorgan comorbidity due to involvement of the gastrointestinal tract, cardiovascular, coagulation, nervous, endocrine, and immune systems. These multiple manifestations are due to systemic viremia and an abnormally activated overactive immune response. These two mechanisms underlie the pathogenetic damage to key endocrine glands in SARS-CoV-2 infection.

The leading pathophysiological mechanisms of acute Covid-19 are as follows: direct viral toxicity; endothelial dysfunction and microvascular damage; immune system dysregulation with stimulation of a hyperinflammatory state; hypercoagulation

with in situ formation of both microthrombi and macrothrombi; ACE2 pathway incompleteness and hormonal dysfunction [18].

MERS is characterized by high mortality, but unlike SARS viruses, it does not cause endocrine damage. Why this occurs cannot be answered. It is known that receptors for the enzyme dipeptidyl peptidase-4 are the gateway for MERS-CoV entry into the cell. Regardless of their expression in endocrine gland tissues, this type of coronavirus has not been detected in any endocrine gland by clinicopathological, immunohistochemical autopsy studies, or structural molecular analysis [19].

Importance of hypothalamic-pituitary-adrenal axis hormones for survival from COVID-19

Although there are no sufficient observations yet, it is hypothesized that in the setting of COVID-19, both hypothalamic and pituitary tissue may be attacked, either simultaneously or separately, because they express the two viral receptors ACE2 and TMPRSS2 and because the virus possesses marked neurotropism. Hypothalamic-pituitary parenchymal tissue can be damaged directly by the toxic action of the virus at the level of the hypothalamus and/or indirectly, due to de novo-onset autoimmune hypophysitis, as a result of the pathologically activated hyperimmune response of the virus. Disturbances occur in central regulatory homeostasis and the hormonal function of the hypothalamus with temporary or permanent hypothalamic-pituitary dysfunction.

Computed tomography and magnetic resonance imaging studies present evidence of brain damage with subsequent serious complications. Wei et al. examined pituitary autopsy specimens and found that the number of pituitary somatotroph, thyrotroph, and corticotroph cells was reduced and showed changes characteristic of acute damage, such as edema and neuronal degeneration. These findings are consistent with hormonal evidence of reduced serum levels of growth hormone (GH), thyroid stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH) [20]. Secondary hypocorticism and decreased body response to stress occur.

The onset of adrenocortical insufficiency predisposes the fate of patients with Covid toward decreased survival. Administration of adequate doses of glucocorticoids is essential to overcome hypocorticism and maintain glucose and electrolyte homeostasis, adaptation to stress, and magnitude of the immune response [21].

Hormones of the pituitary-hypothalamic axis play an essential role in the modulation of the immune response to virus susceptibility.

High levels of inflammatory cytokines such as interleukins (IL) IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) are known to activate the pituitary-hypothalamic-adrenal axis in the earliest stages of viral infection by stimulating adrenal glucocorticoid hormones (mainly cortisol) to suppress the aggressive inflammatory attack of viral infection by activating the immune response [22]. Proinflammatory cytokines and hypercortisolemia alter the reactivity of acquired cell-type immunity from Th1/proinflammatory to Th2/anti-inflammatory type. The adaptive response of the organism against the virus is determined by the synergic action of the adrenal hormones: cortisol, adrenaline, and noradrenaline. They have a decisive effect in the body's battle against COVID-19.

The assumption of an autoimmune genesis of the damage was suggested by Pal et al. They found that SARS-CoV and SARS-CoV-2 express specific peptides that show amino acid homology to fragments of ACTH. They hypothesized that antibodies targeting SARS-CoV-1 and SARS-CoV-2 could also target endogenous ACTH as cross-reactive antibodies and trigger a pathological immune response [14]. Although purely speculative, this response could be viewed as an adaptive pathological mechanism by which the virus implements its immunoinvasive strategy to block the ACTH response to cortisol secretion from the adrenal glands [15]. On the other hand, this mechanism could be a prerequisite for unlocking secondary adrenal insufficiency. The mechanism can only be speculated because ACTH and cortisol levels are not routinely tested in patients with Covid-19 [16].

It has now become clear that COVID-19 is not just pneumonia. There is a wide variety in the clinical presentation of the disease, including cytokine storm, thromboembolism, and extreme hypertension, which cause polyorgan failure and death in some of the affected individuals. There are,

broadly speaking, three main pathophysiological mechanisms that determine the course and progression of COVID-19. The first of these boils down to the binding of SARS-CoV-2 to its ACE-2 receptor, leading to a decrease in its concentration with a predominant ACE response and the realization of its effects. The second is associated with the involvement of RAAS with a predominant effect of angiotensin, which is one of the most potent vasopressor agents, and attenuation of the action of Ang-(1-7). The third is modulation of the pituitary-hypothalamic-adrenal axis response in the direction of reduced adaptation of the organism to stress and development of secondary hypocorticism. The complexity of these disorders makes the endocrine system easily vulnerable to the action of SARS-CoV-2 due to triggering cytotoxic tissue damage or activating a hyperimmune response, thus causing autoimmune problems or hyperinflammation. The most significant complication is adenohypophysitis, combined with partial hypopituitarism, hypothyroidism, and hypocorticism. A good understanding of these processes allows the application of adequate treatment with glucocorticoids to increase the body's resistance to stress and replace hypocorticism.

Conclusions

Comorbidities of endocrine-metabolic diseases such as diabetes or obesity increase the risk of acute onset of vascular endothelial damage, hypercoagulability, and proinflammation or cytokine storm and potentiate the onset of multi-organ failure, which also determines disease outcome.

A detailed study of the complex pathophysiological mechanisms associated with COVID-19 infection reveals the role of altered RAAS activity triggered by viral-receptor modulation, with the predominance of ACE and angiotensin II. Subsequent vascular endothelial, metabolic, and hormonal disturbances result from complex hormonal disturbances, of which dysregulation of the hypothalamic-pituitary-adrenal hormonal axis is of greatest importance. Increased ACE production, RAAS reactivity, and hypocorticism underlie the critical course of COVID infection and determine the outcome of the disease in terms of survival.

References

1. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation report – 51. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200816-covid-19-sitrep-209.pdf
2. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-CoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5(4)536-44.
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223): 507-13.
4. Lu R, Zhao X, Li J, Niu P, Bo J, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224): 565-74.
5. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. Proc Natl Acad Sci USA 2020;117(17):9241-43.
6. Li F. Structure, function and evolution of coronavirus spike proteins. Annu Rev Virol. 2016;3(1):237–61.
7. Walls A, Park Y, Tortorici M, Wall A, McGuire A, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;181(2):281-92.
8. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181(2):271-80.
9. Rockx B, Kuiken T, Herfst S, Bestebroer T, Lamers MM, Oude Munnink BB, et al. Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model. Science. 2020;368(6494):1012-15.
10. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013;495(7440):251-54.
11. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-37.
12. Santos RA, Ferreira AJ, Verano-Braga T,

Bader M. Angiotensin-converting enzyme 2, angiotensin-(1-7) and Mas: new players of the renin-angiotensin system. J Endocrinol. 2013;216(2):R1-R17.
13. Guy JL, Lambert DW, Warner FJ, Hooper NM, Turner AJ. Membrane-associated zinc peptidase families: comparing ACE and ACE2. Biochim Biophys Acta. 2005;1751(1):2-8.
14. Santos RA, Simoes e Silva AC, Maric C, Silva DM, Machado RP, de Buhr I, et al. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. Proc Natl Acad Sci USA. 2003;100(14):8258-63.
15. Horiuchi M, Akishita M, Dzau V. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. Hypertension. 1999;33–2№:613-21.
16. Kuba K, Imai Y, Ohto-Nakanishi T, Penninger J. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacol Ther. 2010;128(1):119-28.
17. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24(1):422-26.
18. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. Am J Pathol. 2007;170(4):1136-47.
19. Alsaad KO, Hajeer AH, Al Balwi M, Al Moaiqel M, Al Oudah N, Al Ajlan A, et al. Histopathology of Middle East Respiratory Syndrome coronovirus (MERS-CoV) infection-clinicopathological and ultrastructural study. Histopathology. 2018;72(3):516-24.
20. Wei L, Sun S; Zhang J; Zhu H; Xu Y; Ma Q, et al. Endocrine cells of the adenohypophysis in severe acute respiratory syndrome (SARS). Biochem Cell Biol. 2010;88(4):723-30.
21. Lisco G, Tullio A, Stragapede A, Solimando A, Albanese F, Capobianco M, et al. COVID-19 and the Endocrine System: A Comprehensive Review on the Theme. J Clin Med.2021;10(13):2920-27.
22. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020;34(2):327-31.