Clinical and Experimental Health Sciences

Presumptive Molecular Interconnections Between COVID-19 And Huntington's Disease

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ABSTRACT

Objective: The healthcare system worldwide has faced unparalleled challenges as a result of the coronavirus disease of 2019 (COVID-19) pandemic. While respiratory tract disease is the most common symptom of COVID-19, there is increasing evidence of neurological damage caused by the virus. To guide the clinical management of the disease, it is essential to elucidate the mechanisms underlying the pathophysiology of COVID-19. Various research indicate that COVID-19 patients exhibit reduced levels of brain-derived neurotrophic factor (BDNF), which is also a hallmark of Huntington's disease, a neurodegenerative disorder. The objective of this study is to investigate the possible links between COVID-19 and Huntington's disease. This aim is motivated by the need to guide the clinical management of COVID-19, especially given the increasing evidence of neurological damage caused by the virus, including reduced levels of BDNF, a hallmark also observed in Huntington's disease.

Methods: The comprehensive literature review conducted for both COVID-19 and Huntington's disease, focusing on the genes associated with both conditions. These genes were then analyzed using the STRING database to determine protein-protein interactions, aiming to elucidate the mechanisms underlying the pathophysiology of COVID-19 and its potential connections to Huntington's disease.

Results: The outcomes of the study indicate that there could be molecular-level interactions between COVID-19 and Huntington's disease, based on the literature research and STRING database analysis. Although the primary mechanism behind these interactions is not yet fully understood, the hypothesis suggests that BDNF and its high-affinity receptor TrkB may play a crucial role. Additionally, the study highlights olfactory dysfunction as a common symptom of COVID-19, which is also linked with various neurodegenerative conditions, including Huntington's disease.

Conclusion: This work emphasizes the connection between COVID-19 and neurodegenerative diseases, particularly through the lens of olfactory dysfunction, a common symptom shared by COVID-19 and Huntington's disease. The potential molecular interactions observed suggest that COVID-19 could exacerbate neurodegenerative processes. This underscores the critical need for further research focused on olfactory dysfunction as a key symptom, to better understand and manage the implications of COVID-19 in patients with neurodegenerative conditions.

Keywords: Olfactory dysfunction, amyloid – β, α-synuclein, BDNF, ACE2, NTRK2

1. INTRODUCTION

The rapid transmission and high mortality rate associated with SARS-CoV-2, the virus responsible for COVID-19, has turned this outbreak into a global emergency. Respiratory droplets are the main mode of transmission for the virus, and it can be disseminated by individuals who are presymptomatic, asymptomatic, or symptomatic (1). The prevalent symptoms of the virus consist of dry cough, shortness of breath and fever. Additionally, there may be radiographic and laboratory anomalies, such as elevated lactate dehydrogenase and lymphopenia (2). Severe COVID-19 cases have been linked to unregulated inflammatory responses, where proinflammatory cytokines are released, leading to abnormalities in granulocytes, monocytes, and lymphocytes, as well as lymphocyte dysfunction and lymphopenia (3). Additionally, there is growing evidence of neurological damage caused by COVID-19, highlighting the need to better understand the disease's pathophysiology (4).

Newer research indicates that the angiotensin-converting enzyme 2 (ACE2) is the functional receptor for SARS-CoV-2 in human body. ACE2 is an enzyme that plays a role in normal brain function and the production of neurotrophic factors such as BDNF through the mediation of proteins like Mas which is a critical component of the renin-angiotensin system

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(RAS), specifically within the ACE2/Ang-(1-7)/Mas axis that is known to exert protective effects in the brain (5,6). BDNF is essential for neural development, neurogenesis, and the protection against neurodegeneration, and plays a role in mood regulation and cognitive performance. Decreased ACE2 activity or expression can result in disruptions to normal neurological and mental function, with long-term consequences (7).

SARS-CoV-2 enters cells by employing ACE2 as a coreceptor, and the viral coat expresses a protein called spike (S protein), which binds with high affinity to the extracellular domain of ACE2 (8). Previous studies have shown that ACE2 is linked to a decrease in BDNF levels(9)and it is thought that SARS-CoV-2 downregulates ACE2 in cells (10). This downregulation could result in decreased BDNF levels in the brain, leading to neurodegeneration and mental disorders such as anxiety, depression, and cognitive impairment(10). In 2020, a study revealed that individuals with moderate to severe COVID-19 had reduced levels of BDNF compared to those with mild symptoms, and as patients recovered, their BDNF levels returned to normal. (11).

Both BDNF and its high-affinity receptor (TrkB) are expressed not only in the central nervous system (CNS), but also in numerous peripheral organs (12). In experimental cases of and traumatic injury of the brain and spinal cord, the activation of TrkB by BDNF exhibits neuroprotective properties by promoting synaptic plasticity and cellular survival (13). On the other hand, mutations in TrkB have been linked to various neurological disorders (14,15).

Huntington's disease (HD) is a neurodegenerative disorder characterized by movement abnormalities, cognitive impairment, and psychiatric symptoms. The worldwide prevalence of HD is 2.7 per 100,000, with higher rates observed in Europe, North America, and Australia (5.7 per 100,000) compared to Asia (0.4 per 100,000) (16). HD is the result of a pathogenic expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeat in the huntingtin (HTT) gene on chromosome 4, with 36 repetitions being the threshold for developing the disease (16). Various mechanisms, including the direct effects of the exon 1 mHTT fragment, are responsible for neuronal dysfunction and death caused by mutant huntingtin (mHTT). mHTT's proclivity for forming aberrant aggregates, and its effects on cellular proteostasis, mitochondrial function, and synaptic function (17). HD patients often exhibit atrophy, or shrinkage, of the caudate nucleus and putamen in the dorsal striatum, which are brain regions involved in motor control and cognitive processing, leading to severe motor dysfunction, behavioral disorders, and cognitive impairment (18,19).

The significance of BDNF lies in its role in promoting neuron survival, and its relation to the pathogenesis of HD has been the subject of extensive research. Reduced levels of BDNF in the striatum have been hypothesized to explain neuronal loss in HD (20). In 2008, a study demonstrated a significant decrease in both BDNF mRNA and protein levels in the cortex of patients with HD. The study also found low TrkB related mRNA levels in caudate tissue (21). This suggests that imbalanced neurotrophic receptor signaling is present in HD. The loss of BDNF has been extensively studied and has been shown to play a key role in the degeneration of medium spiny neurons (MSNs) in HD (22).

NTRK2, also known as TRKB, is the primary receptor for BDNF. In HD-MSNs, there is a downregulation of NTRK2, suggesting that mHTT might cause a decrease in BDNF signaling at the receptor level (22). Studies on HD mouse models have shown a reduction in retrograde movement of TrkB vesicles into striatal dendrites, as well as reduced BDNF/TrkB-induced signaling via ERK phosphorylation and c-fos activation (22,23). This change in transport could exacerbate BDNF-TrkB survival signaling within the corticostriatal connection, which is particularly impaired in HD (23). HD patients exhibit reduced expression of NTRK2 encoding the TrkB receptor (24).

In summary, HD is caused by a genetic mutation in the HTT gene, leading to neuronal dysfunction and death through various mechanisms. BDNF has been extensively studied in relation to HD pathogenesis, with reduced levels of BDNF in the striatum hypothesized to explain neuronal loss. The downregulation of NTRK2 at the receptor level, the primary receptor for BDNF, in HD-MSNs implies that mHTT could cause a reduction in BDNF signaling. Reduced retrograde movement of TrkB vesicles into striatal dendrites exacerbates BDNF-TrkB survival signaling impairment within the corticostriatal connection in HD. HD patients exhibit reduced expression of NTRK2 encoding the TrkB receptor.

2. METHODS

A comprehensive review of the literature was carried out for both conditions by using the keywords; COVID-19, Huntington's disease, SARS-CoV-2, and Brain-Derived Neurotrophic Factor. The genes linked to the developmental stages of each disease were identified, extracted, and analyzed from the genes mentioned in the papers. The identified genes were thoroughly studied, including their roles, the molecular paths they are entitled with, and molecular backgrounds. Using this dataset, the genes linked with COVID-19 and HD were categorized and presented in a list. To determine the protein-protein interactions, these genes have been added to the STRING ver.12.0 database (25). By combining known and anticipated interactions from a range of sources, the database and online resource STRING generalizes access to protein interaction data. Based on comprehensive orthology classifications and a consistent body of fully sequenced genomes, the underlying infrastructure enables the transfer of interaction evidence between species. While the primary purpose of creating the resource was for protein interaction analysis, it has also demonstrated success in other fields, including comparative genomics, phylogenetics, and network studies. Access to the database backend through programming and the availability of compressed download files enable the aforementioned

applications. Predicted functional partners were displayed following the initial input. The selection of network settings involves representing various forms of evidence as network edges, with experiments, databases, text mining, co-expression, location, gene fusion, and co-occurrence being the active sources of interaction.

3. RESULTS

It is hypothesized that molecular interactions between COVID-19 and HD could occur, potentially involving BDNF and its receptor NTRK2. COVID-19 disrupts the BDNF pathway, leading to low BDNF levels which have been observed in COVID-19 patients. Low BDNF and NTRK2 levels are also indicative of HD. In addition, the presence of olfactory dysfunction as a symptom of COVID-19 could serve as a clinical indicator of underlying neurodegenerative disorders, including HD. While the precise mechanisms of these potential interactions remain unclear, understanding their possible links could aid in the development of effective therapies for both diseases (26).

3.1. Molecular Mechanisms and Physiology of the Related Genes

Initially, COVID-19 was believed to only affect the respiratory system, but it has since been discovered that it can impact other systems, including the nervous system. One common symptom is anosmia, or the loss of smell and taste, which can occur even without other severe symptoms. This indicates that SARS-CoV-2 interacts with olfactory cell populations in unique ways (27). The olfactory epithelium, a complex tissue consisting of multiple cell types, can be affected by conductive, sensorineural, or both processes leading to olfactory disorders (OD). Direct injury to sensory neuronal systems from viruses and head trauma is a typical cause of sensorineural disease (28). While many viruses can cause OD, the high prevalence and quick recovery time associated with SARS-CoV-2 infection suggest a different mechanism. Studies have shown that OD develops early and recovers quickly during COVID-19, revealing unique interactions between the virus and the OD (29,30). The understanding of COVID-19's effects on the nervous system is still evolving, but the growing evidence suggests it goes beyond respiratory symptoms.

SARS-CoV-2 enters host cells through the ACE2 receptor, which is primed by the serine protease TMPRSS2 (31). The expression of ACE2 is strongly associated with olfactory dysfunction (OD) during SARS-CoV-2 infection. The virus can reach the central nervous system (CNS) through transneuronal and hematogenous pathways. In 2020, a study identified SARS-CoV-2 specific antigens and RNA in the cerebrum of COVID-19 patients, indicating the virus's ability to enter the CNS (32). However, it remains unclear whether SARS-CoV-2-induced OD is caused by direct viral infection of olfactory neurons or not (33). While early studies suggested direct infection of olfactory neurons, recent evidence indicates that ACE2 is not expressed in the olfactory bulb's olfactory neurons (33). Brann et al. demonstrated high levels of ACE2 and TMPRSS2 expression in SUS cells, progenitor/stem cells, and Bowman's glands, suggesting that the virus may enter olfactory neurons indirectly through these cells (33).

CNS injury during COVID-19 infection can be caused by two main factors. The first factor is the ACE2 receptors, which are expressed in many neurons and non-neuron cells, including astrocytes, endothelial cells, olfactory-bulb vascular pericytes, and oligodendrocytes (32–35). Coronaviruses can directly attack these cells and destroy the blood-brain barrier, causing damage and releasing proinflammatory mediators. The damage of blood vessels around the olfactory bulb can lead to insufficient blood supply and damage to neurons, resulting in olfactory dysfunction (35,36). The second factor is associated with the immune system's dysfunction causing excessive synthesis of cytokines and the cytokine storm induced by SARS-CoV-2 and immune-mediated toxicity can compromise the blood-brain barrier, resulting in secondary harm. Elevated levels of IL-6 in acute COVID-19 disease have been linked to an augmented permeability of the blood-brain barrier (37,38).

New studies have revealed links between COVID-19 and neurodegenerative diseases. The spike protein receptor binding domain of SARS-CoV-2 binds to heparin and heparin binding proteins, leading to abnormal aggregation of potentially pathogenic proteins such as TDP-43, α-synuclein, amyloid-β, and tau (39,40). Mechanisms resembling this phenomenon have also been observed in HSV-1 and Alzheimer's disease. In the latter case, HSV-1 is known to accelerate the aggregation of amyloid-β (39). Viruses have been shown to interfere with mitochondrial and lysosomal functions and autophagy, all of which are implicated in neurodegenerative diseases (41). Recent studies have revealed a possible association between COVID-19 and neurodegenerative diseases (ODs) through altered autophagy, mitochondrial, and lysosomal activities in infected lung cells (42). The spike protein receptor binding domain of SARS-CoV-2 has been found to interact with proteins involved in neurodegeneration, potentially leading to abnormal protein aggregation and neurodegeneration (39,40). Rab7a and NUP62 are two of the most promising interaction candidates between COVID-19 and OD (43). A study conducted in 2020 identified the susceptibility of CNS structures to SARS-CoV-2 and its ability to cause neuronal death, changes in tau hyperphosphorylation, and distribution (44). Molecular-level investigations have identified protein interactions as a link between COVID-19 and olfactory dysfunction. This suggesting long-term inflammation and neuronal death as potential consequences (43).

ACE2 is a functional receptor for SARS-CoV-2 invasion, identified in both in vitro and in vivo experiments. ACE2 expression is linked to the level of virus infectivity, and upon infection, S glycoprotein binds to ACE2 with the aid of TMPRSS2, leading to ACE2 downregulation. ACE2 deficiency

is associated with a decrease in BDNF expression, which was found to be low in SARS-CoV-2 patients and restored during the recovery period. This suggests a higher risk of neurodegenerative diseases in COVID-19 patients due to ACE2 receptor downregulation during infection, which inhibits the BDNF-TrkB pathway (9,45).

Accumulating evidence indicate that BDNF plays a crucial role in the development and onset of HD by facilitating neurogenesis in the human body (46). BDNF is co-localized with huntingtin in 75% of striatal neurons and 99% of pyramidal motor cortical neuron, and it is required for the survival of striatal medium spiny neurons (MSNs) and healthy cortico-striatal synaptic activity (46). However, mHTT, the mutated huntingtin protein, is thought to prevent BDNF from reaching the striatum by interfering with its transport and activity-dependent release (46,47). Low levels of BDNF were observed in animal models of HD and post-mortem human HD brains, indicating its crucial role in MSN degeneration (21). A 2018 study revealed that the downregulation of BDNF signaling in HD-MSNs may be induced by mHTT at the receptor level, as levels of NTRK2 (TrkB), the main receptor for BDNF, were found to be down-regulated in the striatal neurons of HD-MSNs (21,22). Impairment of TrkB receptors was suggested to mediate postsynaptic dysfunction of MSNs in mouse models of HD, although changes in NTRK2 mRNA levels were not detected in HD mouse models (22). Furthermore, another study in 2018 indicated the protective potential of NTRK2 in HD and suggested that targeting BDNF receptors as a treatment method for HD may help preserve frontal gray matter (48).

3.2. Interconnection of COVID-19 and Huntington's Disease molecular mechanisms

ACE2 is known to serve as a functional receptor for coronaviruses, particularly the COVID-19 virus but it also plays an important role in regulating normal brain function and the release of neurotrophic factors such as BDNF through the mediation of the Mas protein (5,6). Studies have shown that decreased activity or reduced expression of ACE2 due to natural or acquired accidents can impair normal neurological and mental function, leading to long-term effects (49). BDNF is heavily associated with brain plasticity, which is crucial for learning and memory, and is widely distributed in neuronal cell bodies. The signaling pathway of BDNF is initiated by binding to its high-affinity receptor TrkB and can act through autocrine and paracrine mechanisms depending on the location of cell surface receptors (50). It is hypothesized that COVID-19 infection inhibits ACE2 and its downstream effects in the brain, resulting in a decrease in BDNF levels (10). Additionally, the mutant huntingtin protein is believed to be involved in the transport and activity-dependent release of BDNF, and its presence can prevent BDNF from reaching the striatum in HD (46,47). Research has shown low levels of BDNF in animal models of HD and post-mortem human HD brains, suggesting its crucial role in MSN degeneration (21). Therefore, regulation of BDNF and its receptors is essential for both COVID-19 and HD. Targeting the BDNF signaling pathway may represent a potential therapeutic approach for the treatment of both disorders.

Separate collections of genes related to the onset of SARS-CoV-2 infection and HD were compiled based on insights gleaned from the literature. After that we used STRING database to be able to comprehend their protein-protein interactions belonging to these genes. Protein–protein interactions were as we assumed and supporting our hypothesis. Fig 1 provides compelling evidence of protein-protein interactions between these two diseases through multiple genes. The genes depicted in Fig 1 served as inputs, and the predicted associations are displayed accordingly. In line with the results obtained from this figure, COVID-19 and HD related genes are associated directly with BDNF via interactions, co-expression, and text mining. Apart from the protein-protein interaction network, the co-expression of these genes was also examined using the STRING database. The results are shown in Fig 2. The heat map in the STRING database represents co-expression levels, with light pink indicating weak co-expression and dark pink indicating strong co-expression. The figure provides valuable information for future research and supports the study's hypothesis. On the left-hand side of the figure, there are light-pink boxes that denote poor co-expressions of specific genes in Homo sapiens. These genes include SNCA and MAPT, SNCA and NTRK2, as well as RAB7A and HTT. Meanwhile, a dark-pink box indicates strong co-expression between MAPT and NTRK2 in Homo sapiens. On the right side of the figure, co-expressions of the same genes among other organisms are also shown, with Mus musculus, Gallus gallus, and Xenopus tropicalis exhibiting co-expression between SNCA and NTRK2.

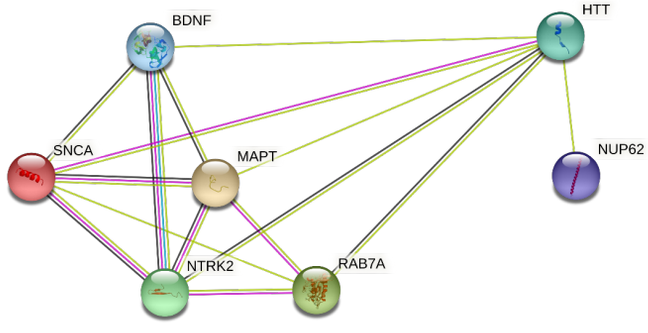

Figure 1. *The generated network of protein interactions by STRING database. This figure displays protein interactions sourced from the STRING database, showcasing the genes associated with both COVID-19 and Huntington's disease. The light-blue lines connecting the genes represent associations based on the curated databases, whereas the pink lines indicate experimentally determined interactions between the genes. Yellow lines demonstrate textmining co-occurrence and black lines point outs co-expression. As it is shown in the figure, the important connection between COVID-19 and Huntington's disease is between HTT, SNCA and BDNF, from curated database, interactions, text mining and co-expression.*

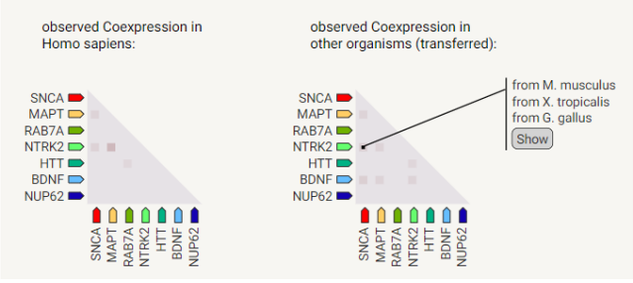

Figure 2. *Data from the STRING database was utilized to conduct gene co-expression analyses for both COVID-19 and Huntington's disease. This figure shows the STRING database results for the co-expression of genes associated with COVID-19 and Huntington's disease. Light-pink boxes on the left side of the figure denote poor co-expressions of the genes SNCA and MAPT, SNCA and NTRK2, RAB7A and HTT in Homo sapiens. Dark-pink box shows strong co-expression between the genes MAPT and NTRK2 in Homo sapiens. The co-expressions of the same genes among the other organisms are presented on the figure's right part. Mus musculus, Gallus gallus and Xenopus tropicalis have showed co-expression between SNCA and NTRK2 The heat map visualizes the co-expression scores obtained from the ProteomeHD database, which were constructed according to the RNA expression patterns and protein co-regulation. These scores were then visualized using the STRING database.*

4. DISCUSSION

COVID-19 was once considered to only influence the respiratory system; however, it now appears to affect a variety of other systems, including the nervous system. Since COVID-19 could be linked to several neurodegenerative conditions, we aimed to examine whether there is a molecular relationship between COVID-19 and HD. According with literature review, several genes linked to HD, including HTT, BDNF, NUP62, and SNCA, and some genes associated with SARS-CoV-2 infection, including BDNF, TrkB, RAB7A, and MAPT, have demonstrated some relationships among each other. Further examination of these relationships through STRING analyses to better understand their protein-protein interactions yielded promising results. As mentioned earlier, the literature research conducted on the genetic and molecular underpinnings of COVID-19 and HD suggests that both conditions could be connected pathophysiologically via the BDNF signaling pathway. After gathering sufficient evidence, the relationship between SARS-CoV-2 infection and another neurodegenerative disorders may be improved in the future aspects of this study.

5. CONCLUSION

In conclusion, this study provides illumination on the intricate correlation between COVID-19 and neurodegenerative disorders, specifically HD, surpassing the initial comprehension of COVID-19 as a respiratory affliction. Our examination, centering on genes associated with both HD and SARS-CoV-2 accentuates a potential pathophysiological connection through the BDNF signaling pathway. Importantly, the presence of olfactory dysfunction, a symptom shared by COVID-19 and diverse neurodegenerative ailments, underscores the significance of these discoveries. This symptom serves as a pivotal point of intersection, suggesting that COVID-19 might exacerbate neurodegenerative processes. Our discoveries emphasize the necessity for additional research into the molecular mechanisms in operation, particularly regarding olfactory dysfunction and its role in the advancement of neurodegenerative diseases within the framework of COVID-19. The comprehension of these associations is crucial for the formulation of targeted treatments and management strategies for patients with neurodegenerative conditions in the era of COVID-19, emphasizing the importance of an interdisciplinary approach in forthcoming investigations.

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