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Mini Review

Physical Exercise, Brain-Derived Neurotrophic Factor and the SARS-CoV-2 Pandemic

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Received: August 02, 2021; **Published:** August 12, 2021

Abstract

In this short communication, the two-fold effect that the SARS-CoV-2 pandemic has on the neuroprotective neurotrophin, brain-derived neurotrophic factor (BDNF) is briefly reviewed: (1) The direct effect of the virus on BDNF itself and (2) the indirect effect, also on BDNF, but through forced quarantine, which takes its toll on physical, mental and emotional health.

Keywords: *Exercise; BDNF; Physical Activity; COVID-19; Pandemic*

Introduction

The body of literature providing evidence of importance and impact of exercise on overall physical and mental health is voluminous [1] and therefore, cannot be overstated. Both physical and mental effects of exercise are inextricably linked, necessitating characterization of the intracellular effects at the molecular level [2-5]. Whether this exercise is typically deliberate (e.g. as in a daily visit to the gym) or incidental (e.g. walking to work every day), both types contribute to better physical and mental health. The pandemic-induced forced lockdowns presented novel challenges in daily coping, whether exercise was deliberate or not.

In this short communication, I will highlight some of the most recent findings on the effects of the SARS-CoV-2 pandemic-induced quarantine on mental and emotional health, with particular focus on brain-derived neurotrophic factor (BDNF). Although such restrictions have never before been experienced in modern times, it would not be too far-fetched to hypothesize that they resulted in decreased levels of hippocampal BDNF. This neurotrophin, well-known to play central and critical roles in memory and cognition, neurodevelopment and neuroprotection [6,7], is up-regulated as a result of physical exercise [2,8-10].

Towards this end, there are two avenues by which BDNF may play a role in a forced quarantine: (1) Direct: What are the effect(s) of the SARS-CoV-2 on the levels of BDNF itself? And (2) Indirect: What are the effect(s) of the imposed restrictions on BDNF levels? Within the context of both questions are the effect of exercise on BDNF levels. The following will elucidate each of these two effects in turn.

The effect(s) of SARS-CoV2 on BDNF levels (Direct)

Although the evidence is not exactly overwhelming, it has been hypothesized that although angiotensin-converting enzyme-2 (ACE2) acts as a receptor for SARS-CoV-2 in respiratory and cardiovascular tissues, it also gains entry into the brain via either the nasal passages

[11] or through one of the several places without a significant blood-brain barrier. The virus becomes physiologically widespread because its primary method of conveyance is the vasculature [12]. ACE2 normally catalyzes the formation of a peptide, called angiotensin (1-7), which then activates Mas protein, which, in turn, participates in the production of BDNF [13]. Numerous studies have implicated BDNF is decreased in depression, stress and anxiety [9] and increases in cognition, while at the same time, contributing to neuronal survival through decreasing oxidative stress, apoptosis and inflammation [13]. Because exercise is a powerful inducer of BDNF [14], the foregoing, therefore, are notable benefits of physical activity [9,15]. Infection by SARS-CoV-2 inhibits ACE2, thereby inhibiting the ACE2-angiotensin (1-7)-Mas pathway leading to BDNF production, which, in turn, contributes to neuronal degeneration.

In addition, it is also possible that indolamine-2,3-dioxygenase, which increases kynurenine metabolites in the brain and, in turn, produces chemokines, such as angiotensin-2, which is allowed to accumulate, because SARS-CoV-2 has inhibited ACE2. These kynurenine metabolites contribute to pro-oxidative and pro-inflammatory [16] stressors and concomitant cognitive decline [17]. Thus, SARS-CoV-2 is a pro-inflammatory agent [12,16,18]. It is noteworthy that several drugs originally used for other purposes, such as schizophrenia, can be neuroprotective: second-generation antipsychotic drugs have been implicated in a neuroprotective role by reversing the chemokine-induced decrease in oxidative enzymes, such as catalases and peroxidases, and thereby decreasing the concentrations of reactive oxygen species [19].

Moreover, if a(n) (elderly) person is on the verge of even the earliest stages of Alzheimer's Disease (Stage 1), SARS-CoV-2 infection could possibly exacerbate the progression of the former; inhibition of ACE2 inhibits its normal kinase-inhibiting activity, thereby leading to the hyperphosphorylation of tau and subsequent microtubule disarray and neuronal degeneration [20].

Fortunately, BDNF production does not solely depend on the ACE2-angiotensin(1-7)-Mas axis [21], as there are numerous other pathways (mitogen-activated protein kinase (MAPK), phosphatydilinositol-3'-kinase (PI-3K/Akt), protein kinas A (PKA)) that also lead to its production ([21] and references cited therein). As long as exercise is maintained, therefore, and unless, SARS-CoV-2 infection is debilitating, BDNF can still be produced via these other pathways.

Finally, peripheral BDNF levels reflect its concentration centrally because it can cross the blood-brain barrier [22]. Therefore, BDNF levels in the brain is consistent with plasma BDNF levels that have been shown to be inversely correlated with SARS-CoV-2 severity [23] and increased in SARS-CoV-2–recovered patients [24].

The effect(s) of imposed restrictions on BDNF levels (Indirect)

The advent of the SARS-CoV-2 pandemic-induced quarantine resulted in home confinement (lock-downs), loss of livelihoods [25], social contact and interactions, medical attention for other illnesses, and diversions (entertainment), increased stress, anxiety, depression [18,26,27], loneliness [28], alcohol abuse [16], suicide [25], domestic violence [29,30] and homicides [31], as well as increased stress, anxiety and depression among health-care workers themselves [32]. Much of the preceding necessarily culminated in less movement, less physical exercise, resulting in threats to both physical and mental health because in light of the previous section, less BDNF is secreted.

Conclusion

Whether physical exercise is deliberate, anything that can increase circulating and central BDNF levels would be conducive to surviving both the direct and indirect effects of SARS-CoV-2 induced forced lockdowns. Although a cliché, even this pandemic cloud has a disproportionately small silver lining: it has and continues to necessitate the characterization and elucidation of viral infection and how the body copes with such infection.

Conflict of Interest

The author declares that there is no conflict of interest.

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Volume 13 Issue 9 September 2021
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