Letter to the Editor

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TANAFFOS

Trimetazidine May Potentially Confer Neuroprotective Effects against COVID-19-Induced Neurological Sequelae via Inhibition of Death-Associated Protein Kinase 1 (DAPK1) Signaling Pathways: An Evidenced-Based Hypothesis

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Dear Editor

COVID-19, the disease caused by Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2), spread quickly across the globe beginning in 2019 and triggered an ongoing worldwide pandemic (1, 2). According to the World Health Organization, as of September 2022, nearly 594 million people have been infected with this disease, and ~6.45 million people have died due to COVID-19 (3). Although other infectious coronaviruses, such as SARS-CoV1 and Middle East Respiratory Syndrome coronavirus (MERS-CoV), caused health problems and complications similar to those caused by COVID-19, such diseases were not classified as pandemics because their contagiousness, pathogenicity, and infectivity were much lower compared to COVID-19 (4-8).

While COVID-19 is known for causing lethal respiratory dysfunction and cardiovascular problems, it is also true that COVID-19 can cause neurological disorders and neurodegeneration (9-12). COVID-19 affects both the central nervous system and the peripheral nervous system (13). Short-term and long-term neurological consequences in pandemics are frequently overlooked, and such under-recognition of neurological manifestations can increase the long-term burden of disease. Thus, it is critical to develop a thorough understanding of the possible mechanisms of neurological damage during disease epidemics or pandemics (14) and evaluate current medications for their potential efficacies.

COVID-19 can cause the induction of neurological dysfunction and neurobehavioral disorders such as stroke, epilepsy, motor-related disorders, cognition impairment, dementia, depression, and anxiety (10, 15). Several lines of indirect evidence and molecular studies suggest that COVID-19-induced neurological disorders may occur due to mitochondrial dysfunction, oxidative stress, inflammation, and apoptosis in neuronal cells; however, the mechanisms of action remain unclear (2, 13, 16, 17). Therefore, it is important to understand the pathophysiology of COVID-19-induced neurological diseases by investigating the molecular mechanisms and pathways of nerve cell death and the subsequent neurological disorders (2, 13, 16-18).

The death-associated protein kinase 1 (DAPK1) signaling pathway is a critical molecular pathway involved in nerve cell death and the occurrence of neurodegeneration (19-22). The DAPK1 protein family consists of five serine/threonine (Ser/Thr) kinases that are involved in multiple strategic cellular processes, such as apoptosis and autophagy (21, 23-25). Overexpression of the DAPK1 signaling cascade is associated with neuronal cell death and neurodegenerative events (22). DAPK1 regulates cell death-related pathways via a mechanism that likely involves activation of mitochondrial dysfunction, oxidative stress, and inflammation in neuronal cells (22, 26, 27). Therefore, blocking these strategic cascades and disrupting DAPK1-related cell death could be an effective treatment for reducing neuronal loss and could be a therapeutic approach in neurodegenerative events (21, 26-29). While the DAPK1 signaling pathway is a prominent feature in the molecular biology of neurodegeneration, its involvement in COVID-19-associated neurobehavioral dysfunction and neurodegeneration and its potential role in the pathophysiology of coronavirus-induced neurological dysfunction is unknown.

To effectively manage COVID-19-induced neurological dysfunction, new advancements should focus on eliciting a neuroprotective role (7, 30, 31). Furthermore, the proposed drugs should target the underlying mechanisms of COVID-19-induced neurological dysfunction and neurodegeneration such as mitochondrial dysfunction, oxidative stress, inflammation, and apoptosis in neuronal cells (7, 30, 31). Additionally, candidate agents should target the DAPK1 signaling pathway to provide neuroprotective effects (7, 30, 31).

Trimetazidine (TMZ) has neuroprotective effects (32, 33); as such, TMZ could be considered a candidate compound with potential efficacy for the treatment of the SARS-CoV-2-induced neurodegeneration and neurological sequelae. TMZ is an approved drug for treating angina pectoris in Europe and has anti-ischemic (anti-anginal) properties (32-34). Figure 1 illustrates the main molecular pharmacological mechanisms of TMZ, which cause antioxidant, anti-inflammatory, and anti-apoptotic effects (34, 35). TMZ has a neuroprotective role in neurodegenerative events in various diseases such as Alzheimer's disease, epilepsy, amyotrophic lateral sclerosis, and retinal degeneration (34, 36-38). The effects of TMZ against multiple types of stroke have been investigated in both animal and human studies (33, 39). Several studies indicated that TMZ can act as a neuroprotective agent against ischemia events (33, 40). Additionally, TMZ can modulate neurobehavioral changes in subjects with depression, psychosis, and psychomotor disturbances and can modulate brain serotonin and dopamine levels (41-43).

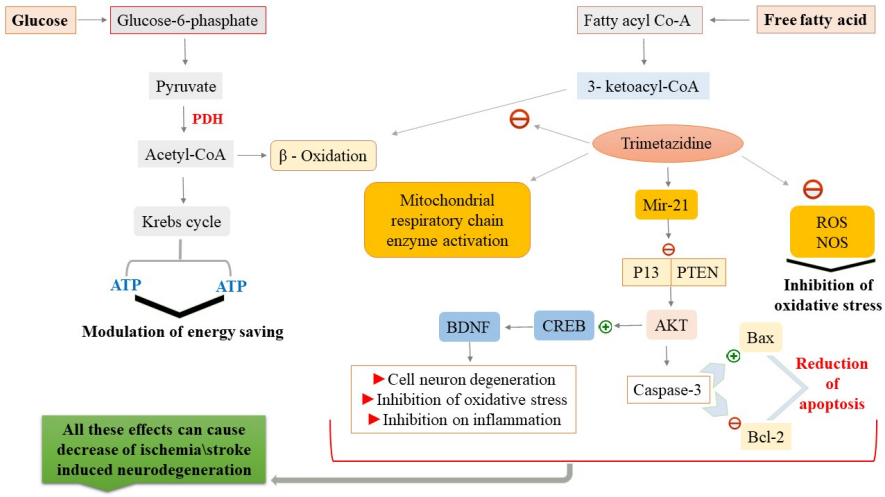

Figure 1. Trimetazidine: possible mechanisms of neuroprotection in Covid-19-induced stroke. A) Trimetazidine inhibits mitochondrial 3-ketoacyl coenzyme A thiolase, thereby decreasing oxidation of long-chain fatty acid, but not glycolysis in the myocardium. The decreased long-chain fatty acid β-oxidation is compensated by increased use of glucose, preventing a lowered myocardial pH, and modulating energy saving. B) Trimetazidine promotes Mir-21, which leads to neuroprotection by inhibiting the PI3/PTEN signaling pathway and preventing the activation of AKT/CREB/BDNF. C) Trimetazidine inhibits ROS and NOS production.

PDH: Pyruvate Dehydrogenase, PTEN: Phosphatase and tensin homolog, PI3: Phosphatidylinositol-3-kinase, AKT: protein kinase B, CREB: cAMP response Element Binding Protein. BDNF: Brian Derived Neurotrophic Factor. ROS: Reactive Oxygen Species. NOS: Nitrogen-Oxygen species.

While several studies have reported the effect of TMZ on ischemia and its neuroprotective effects, no studies have investigated whether TMZ improves the neurodegenerative symptoms of COVID-19, induces neuroprotection against COVID-19-induced neurodegeneration, or involves intracellular signals. Based on previous studies, TMZ may act via the DAPK1-related cell death pathway in preventing ischemia in patients with COVID-19. We hypothesize that TMZ may provide protective effects against COVID-19-induced neurological disorders and neurodegeneration, and these neuroprotective effects are likely modulated via the inhibition of DAPK1-related cell death pathway, which has a critical role in neurodegenerative events (Figure 2).

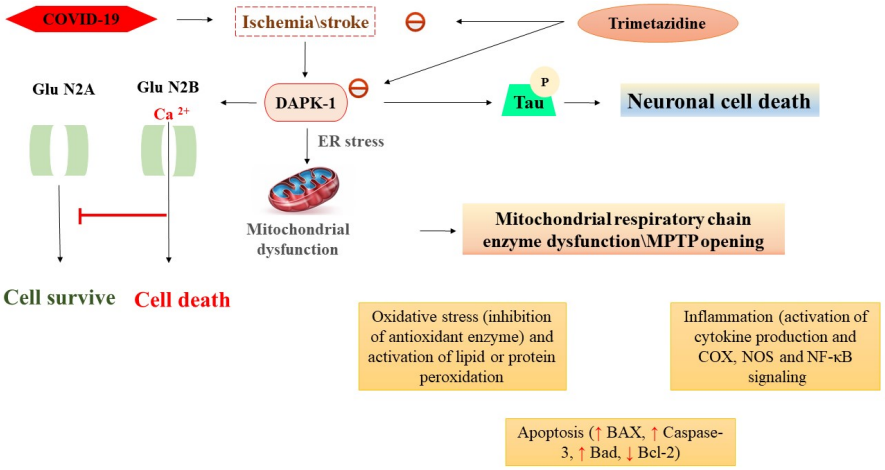

Figure 2. Proposed protective effects of trimetazidine against COVID-19-induced neurodegeneration and neural dysfunction. COVID-19 likely causes activation of DAPK1. DAPK1 activation leads to activation of glutamate receptors, such as GluN2A and GluN2B, which disturbs the balance of intracellular Ca^{+2} levels, causing neuronal cell death. DAPK1 activation also causes activation (phosphorylation) of Tau protein, which is associated with neurobehavioral deficits and neurodegeneration. In addition, DAPK1 activation causes mitochondrial dysfunction, which leads to apoptosis, necrosis, and autophagy.

Moreover, as TMZ inhibits oxidative stress, inflammation, and apoptosis in brain cells, we hypothesize that it would inhibit neurodegeneration and organ damage caused by SARS-CoV-2 infection. We believe that studies in both animal models and human subjects are warranted to evaluate whether TMZ has neuroprotective effects against COVID-19-induced neurodegeneration.

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