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Correspondence



A molecular study of aryl hydrocarbon receptor activation in COVID 19 associated cognitive impairment – Correspondence

Dear Editor,

Evidence suggests that SARS-CoV-2 is linked to cognitive impairment (CI) that may be objectively assessed after acute sickness. However, this emerging ailment's scope, course, and etiology are all unknown. Anti-viral immunity and intrinsic cellular mechanisms are compromised when aryl hydrocarbon receptor (AHR) activation is prominent. This results in an increase in Zika and dengue virus multiplication. AHR inhibition by drugs reduced Zika and dengue infectivity in vitro and restricted Zika virus replication and related pathophysiology in a pre-clinical experiment. As a result of these findings, we believe that SARS CoV-2 infection activates AHR [1]. Therefore, we studied the possible endogenous ligand or pathway and AHR activation-mediated cognitive impairment.

Cognitive impairments are significantly influenced by the degree of acute COVID-19 illness and its associated consequences. Severe cases (hospitalization-required cases) are susceptible to direct and indirect causes of COVID-19-associated brain damage, notably hypoxia, and the systemic inflammatory and immunologic response to SARS-CoV-2. Conversely, there is a risk of brain deterioration and cognitive abnormalities even in mild and moderate instances of COVID-19 that do not need hospitalization [2]. In such circumstances, the causes of brain damage may be studied without the confounding effects of severe illness and its sequelae.

In COVID-19 infection, even in patients with mild symptoms, the kynurenine pathway (KP) is abnormally regulated. As a result, researchers are looking at the KP and the dynamic linkages in mild to moderate cases of COVID-19 that have been infected with SARS CoV-2. Research found that KP activity to be related to mild cognitive loss, suggesting a possible causative relationship, thus identifying it as a biomarker and treatment target for the condition [3]. In addition, KP-associated cognitive impairment has been found in other viral diseases, like HIV, MERS, SARS, and influenza. Based on the existing understanding of the KP and well-established data on IFN-mediated pathways, the mechanism behind the cause of cognitive decline is conceivable conceptually, as we have demonstrated in our work. Furthermore, due to its role as an AHR activator and monocyte/macrophage mediator, KP activation is important in biology and pathophysiology.

Kynurenine has been determined to be an activator of the aryl hydrocarbon receptor [4]. The ligand-activated transcription factor AHR controls multiple immunological and inflammatory response components. Tumor-derived metabolites or viral infection-induced activation of AHR disrupt development of protective immunity. Type I interferons (IFN-I) are suppressed by AHR, most likely through a negative feedback mechanism because IFN-I stimulates the expression of AHR. Recent research demonstrated that IFN-I-independent and IFN-I-dependent

anti-viral intrinsic and innate immunity were inhibited by AHR activation during Zika or dengue virus infection [5]. In addition to genome-wide transcriptional studies, AHR signaling was significantly elevated in SARS CoV-2-infected individuals with medium and high virus loads [1].

Furthermore, Caspase activation and apoptosis are triggered when AhR is activated in non-neuronal cell populations, resulting in neuronal death and brain damage through increased expression of CYP1 family genes, including CYP1A1, CYP1A2, and CYP1B1. Apoptosis-inducing pathways in neurons activated by AhR activation have been shown to occur in experimental stroke models. Furthermore, a drop in serotonin and melatonin is related to an increase in KP synthesis and activation of AhR. Another possibility is cytochrome P450 (CYP) 1B1-mediated AhR activation that results in decreased melatonin availability. According to researches, melatonin-treated individuals performed much better on the Mini-Mental State Examination and the Alzheimer's Disease Assessment Scale's cognitive subscale. Therefore, a regular evening dose of melatonin strengthens sleep quality and cognitive function in patients with moderate cognitive impairment. AhR activation and pineal melatonin suppression both result in changes in mitochondrial metabolism. AhR activation reduces mitochondrial and cytoplasmic melatonin via raising CYP1B1, lowering sirtuins and SOD, and leading to poor mitochondrial function [6]. In addition, activation of AhR by kynurenine induces activation of COX2-PGE2 and EP4 receptors in NK cells, resulting in suppressed/"exhausted" NK phenotype seen in tumor microenvironment and severe SARS-CoV-2 infection. The COX2-PGE2 pathway inhibits NK cell migration, cytotoxic activity, and IFN generation, with similar effects on CD8⁺ T cells and $\gamma\delta$ T cells (Fig. 1).

In individuals recovering from mild to severe COVID-19, KP is considerably increased, especially when there is a corresponding reduction in minor cognitive loss. Three KP metabolites (3HAA, KYN, and QUIN) have been shown to be related to AHR activation and modest cognitive impairment in bloodstream.

Ethical Approval

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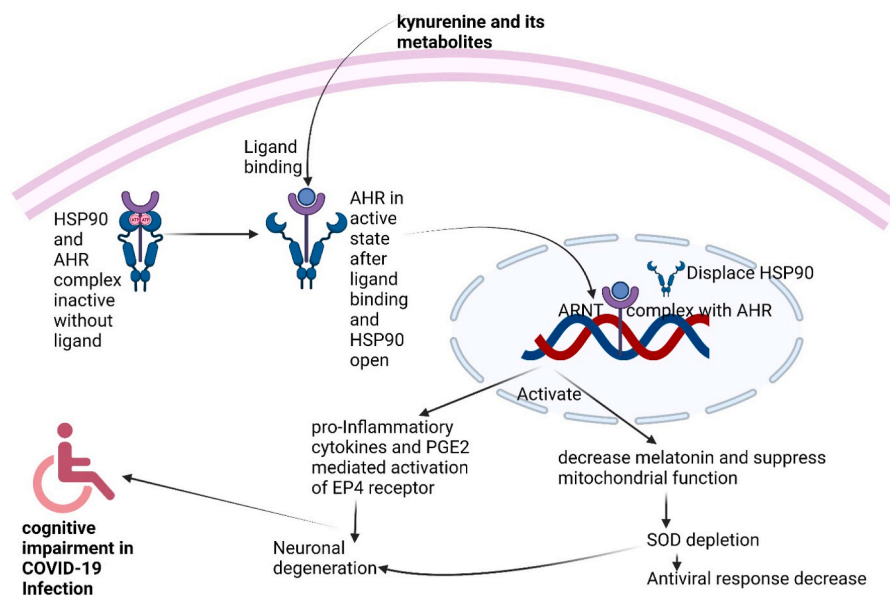


Fig. 1. A molecular study of aryl hydrocarbon receptor activation in COVID 19 associated Cognitive impairment.

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Data Availability Statement

The data in this correspondence article is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature.

Research registration Unique Identifying number (UIN)

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Guarantor

Gaurav Gupta, School of Pharmacy, Suresh Gyan Vihar University, Mahal Road, Jagatpura 302017, Jaipur, India.

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Declaration of competing interest

None.

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Yogendra Singh

Department of Pharmacology, Maharishi Arvind College of Pharmacy, Ambabari Circle, Ambabari, Jaipur, 302023, India

Sachin Kumar Singh

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, 144411, India
Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, Australia

Kamal Dua

Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, Australia
Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, NSW, 2007, Australia

Gaurav Gupta*

School of Pharmacy, Suresh Gyan Vihar University, Mahal Road, Jagatpura, 302017, Jaipur, India
Department of Pharmacology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India

* Corresponding author. School of Pharmacy, Suresh Gyan Vihar University, Mahal Road, Jagatpura, 302017, Jaipur, India.
E-mail address: gauravpharma25@gmail.com (G. Gupta).