





Alterations in Tryptophan Metabolism Affect Vascular Functions: Connected to Ageing Population Vulnerability to COVID-19 Infection?

Arehally M Mahalakshmi¹, Shasthara Paneyala² , Bipul Ray^{1,3},
Musthafa Mohamed Essa^{4,5,6}, Mona Dehghani^{7,8}, Benjamin Heng^{7,8} ,
Gilles J Guillemin^{7,8}  and Saravana Babu Chidambaram^{1,3} 

¹Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India. ²Department of Neurology, JSS Hospital, Mysuru, Karnataka, India. ³Centre for Experimental Pharmacology and Toxicology, Central Animal Facility, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India. ⁴Department of Food Science and Nutrition, CAMS, Sultan Qaboos University, Muscat, Oman. ⁵Ageing and Dementia Research Group, Sultan Qaboos University, Muscat, Oman. ⁶Visiting Professor, Biomedical Sciences Department, University of Pacific, Sacramento, CA, USA. ⁷Neuroinflammation Group, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia.

⁸PANDIS.org.

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CORRESPONDING AUTHOR: Saravana Babu Chidambaram, Professor of Pharmacology, JSS College of Pharmacy, & Coordinator, Centre for Experimental Pharmacology and Toxicology, Central Animal Facility, JSS Academy of Higher Education & Research, Mysuru, Karnataka 570015, India. Email: babupublications@gmail.com

Introduction

The essential amino acid tryptophan is the unique substrate for the biosynthesis of neurotransmitter serotonin, sleep hormone melatonin and co-factor nicotinamide adenine dinucleotide (NAD⁺) through its metabolic pathways.¹ The catabolism of tryptophan by indoleamine 2,3-dioxygenases (IDO1/2) through the kynurenine pathway (KP) leads to the generation of multiple bioactive metabolites referred as kynurenines.^{2,3} Within the central nervous system (CNS), brain cells including glia and neurons produce different kynurenines.⁴ During ageing a shift from the serotonergic to kynurenine pathway progressively occurs in the tryptophan catabolism resulting in an increased activity of the enzyme IDO-1 in turn increases the production of neuroactive KP metabolites.⁵ The progressive alterations of the innate immune system linked to ageing trigger the development of chronic inflammatory cascades referred as ‘inflammaging’ which include astrogliosis, microgliosis and increased production of cytokines like IL-6, IL-1 β , IFN- γ , TNF- α etc. . . .^{2,6} IFN- γ and TNF- α are both know to trigger a strong induction of IDO1 through positive feedback mechanism in older population.⁷ This increased IDO1 activity with age not only results in higher production of kynurenines, but also stimulates inducible nitric oxide synthase (iNOS) activity and increases nitric oxide (NO) production. iNOS is

mainly expressed by activated microglia, astrocytes, endothelial cells and infiltrating lymphocytes.⁸⁻¹⁰

Could IDO-1 Activation be Associated With Vascular Dementia?

The activation of IDO-1 and KP could possibly elicit vascular dementia directly through vasoactive metabolites and/or indirectly by stimulating iNOS through multiple pathways. (1) Several KP metabolites can have a direct effect on blood vessel by eliciting vascular inflammation mediated arterial stiffness and atherosclerosis by binding to aryl hydrocarbon receptors. KYN is an endothelium-derived relaxing factor produced during inflammation.¹¹⁻¹⁶ The basolateral increase of kynurenines especially quinolinic acid at BBB endothelial cells and pericytes also results in local neurotoxicity thus leading to BBB disruption.¹⁷ The excess of quinolinic acid also contribute to the production of β -amyloid and neurofibrillary tangles,^{4,18,19} while amyloid precursor protein and β -amyloid are involved in eliciting endothelium dependent vasoconstriction, reduced cerebral blood flow thus abnormal vascular autoregulation²⁰ leading to neurodegeneration and cognitive impairment.⁴ Alterations in tryptophan metabolism in aged population contribute to the occurrence of vascular impairments, progressive neurodegeneration and in turn cognitive impairment.

(2) As IDO-1 activation leads to iNOS induction, the generated NO reacts with reactive oxygen species (ROS) to produce peroxynitrite (ONOO⁻) which causes oxidative damage to biomacromolecules like lipids, proteins and deoxyribonucleic

#Co-senior authors.



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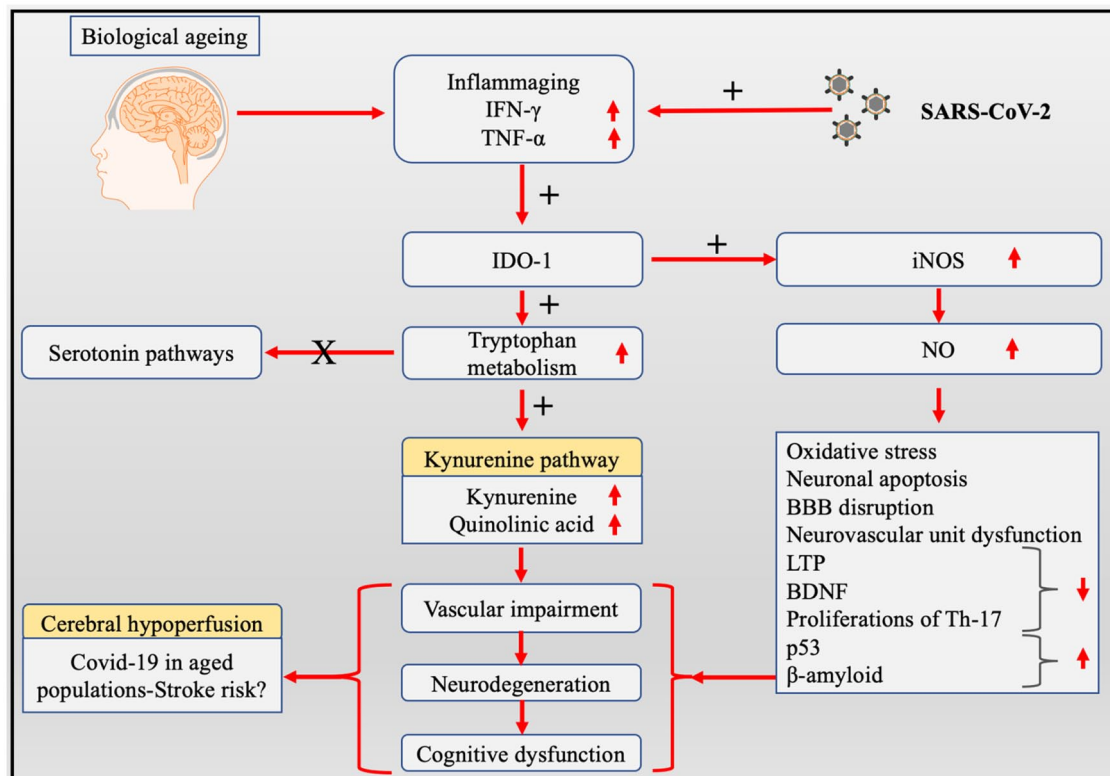


Figure 1. Potential mechanisms of altered tryptophan metabolism induced cerebrovascular and neurodegenerative diseases in Covid-19 aged population.

Abbreviations: BDNF, brain derived neurotrophic factor; IDO-1, indoleamine 2,3-dioxygenases; IFN- γ , interferon-gamma; iNOS, inducible nitric oxide synthase; LTP, long term potentiation; NO, Nitric oxide; TNF- α , tumour necrosis factor-alpha.

acid (DNA) leading to deposition of toxic substances. All those compounds disrupt mitochondrial functions resulting in the failure to meet the biological energy needs for the neuronal homeostasis. The overall effects lead to neuronal apoptosis and blood brain barrier (BBB) disruption contributing to neurovascular dysfunctions.²¹ Additionally, increased levels of NO inhibit long-term potentiation (LTP) formation by decreasing production of Brain derived neurotrophic factor (BDNF), shifting the neuronal stem cells to differentiate into astrocytes thus hindering neurorepair and neurovascular impairment.²²

(3) The excessive formation of NO triggers intracellular accumulation of p53 (pro-apoptotic factor), leading to necrosis of cerebrovascular endothelial cells and vascular smooth muscle cells (VSMCs) and ultimately to neurovascular dysfunctions.²³ (4) iNOS also inhibits proliferation of T cells (Th-17), and increases circulating levels of IL-17, which then activates the Rho A/RHO kinase pathway. The latter inhibits endothelial nitric oxide synthase (eNOS) activity leading to cerebrovascular endothelial cells dysfunction.²³

Is IDO-1 Linked to Vulnerability of Aged Population to COVID-19 Infection?


Severe acute respiratory syndrome coronavirus-2 (SARS Cov-2) infection initially begins with peripheral inflammation and causes activation of endothelial cells leading to BBB disruption

associated with astrogliosis and microgliosis.²⁴ At later stage, this latter events triggers neuroinflammation with increased cytokine/chemokine production, oxidative stress, and the altered immune cells trafficking contribute to further damage of the BBB, generating a strong neuroinflammatory and neurotoxic loop.²⁵⁻²⁷ The dysregulated tryptophan metabolism, especially the high levels of quinolinic acid, in elderly population will amplify the COVID-19 associated risk factors by elevating neuroinflammation,²⁸ compromised the BBB, neurovascular impairments through cerebrovascular endothelial cells and VSMCs dysfunctions.¹⁷ This chain of complex and multifactorial of detrimental events highlights the important effects resulting of the alteration of the tryptophan metabolism in older patients with Covid-19. The viral infection by itself triggers CNS pathologies including strong inflammatory responses, formation of amyloid plaques both leading to increased risk of intracerebral haemorrhage and ischaemic brain damage.^{29,30} The dysregulation of the KP in elderly population could be linked with an higher incidence of cerebrovascular diseases like acute stroke and increased fatality rate in COVID-19 affected elderly population.^{29,31,32} We hypothesise that it is likely that the activation of the kynurenine pathway in elderly COVID-19 patients and survivors ("long-term COVID") could be a major contributor for cerebrovascular damages and a likely therapeutic target (Figure 1).

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ORCID iDs

Shashthara Paneyala  <https://orcid.org/0000-0001-5095-8602>

Benjamin Heng  <https://orcid.org/0000-0002-0247-2920>

Gilles J Guillemain  <https://orcid.org/0000-0001-8105-4470>

Saravana Babu Chidambaram  <https://orcid.org/0000-0003-2357-056X>

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