COVID-19 INFECTION AND NEURODEGENERATION: A POTENTIAL LINK REVEALED BY COMPUTATIONAL SIMULATIONS

Lucija Hok,[a] Hrvoje Rimac,[b] Janez Mavri,[c] Robert Vianello[a,*]

[a] Laboratory for the Computational Design and Synthesis of Functional Materials, Ruđer Bošković Institute, Zagreb, Croatia
[b] Department of Medicinal Chemistry, University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia
[c] Laboratory for Biocomputing and Bioinformatics, National Institute of Chemistry, Ljubljana, Slovenia
* robert.vianello@irb.hr

INTRODUCTION

Although COVID-19 has been primarily associated with pneumonia, recent clinical studies show that ~ 36% of all patients exhibit some of neurological symptoms during the acute phase.[1] Of particular concern are emerging evidences of the SARS-CoV-2 involvement in the development of neurodegenerative diseases, indicating that COVID-19 is likely to have long-term mental health effects on convalescents.[2]

PURPOSE OF THE RESEARCH

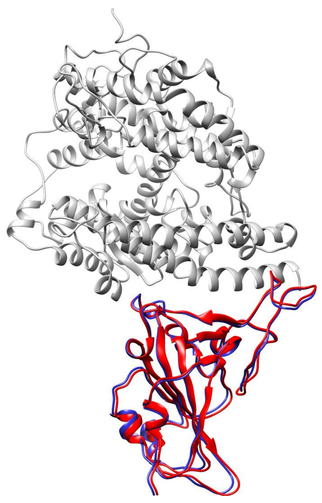
In this research[3] we employed computational techniques to investigate the possibility of the SARS-CoV-2 spike protein to interact with the monoamine oxidase enzymes (MAO) and cause neurodegeneration by misbalancing levels of their neurotransmitters, which is additionally supported by 90% structural similarity between ACE2-spike protein binding region and MAO B.[4]

METODOLOGY

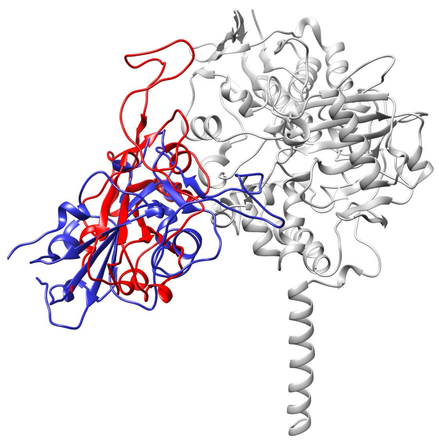
Protein-protein docking studies:	Substrates-enzymes docking studies:	Molecular dynamics simulations (MD):	Solvent-accessible volume estimation:
HDOCK web-server	**AutoDock Vina**	**Amber 16**	**CASTp**

RESULTS

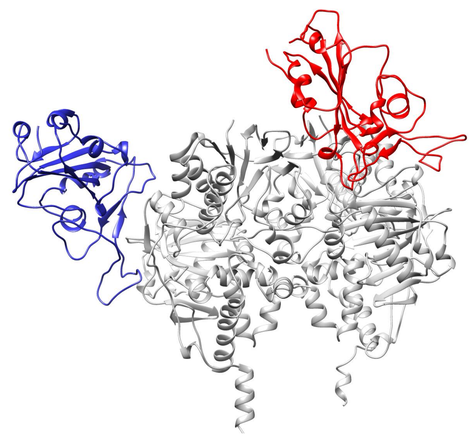
Binding energies of the spike protein from the wild type SARS-CoV-2 and the South African strain B.1.351 to its ACE2 receptor and the MAO A and B enzymes (in kcal mol^{-1})



ACE2 (gray)



MAO A (gray)

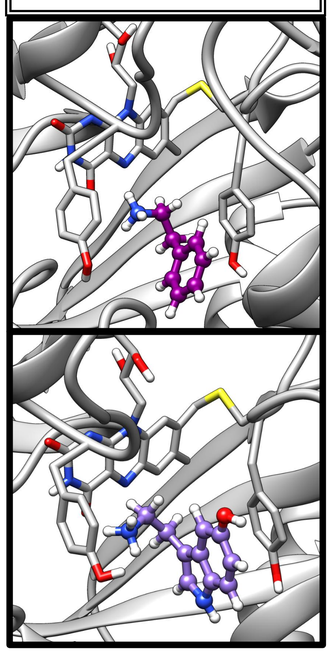


MAO B (gray)

WT (blue)	SA (red)	WT (blue)	SA (red)	WT (blue)	SA (red)
−46.6	−54.8	−38.3	−49.0	−38.1	−62.7

Binding affinities between the MAO isoforms and their physiological substrates following a complex formation with the WT and SA SARS-CoV-2 variants (in kcal mol^{-1})
(Results for the MAO B subunit that does not directly interact with the matching spike protein are given in square brackets)

MAO A



phenylethylamine

−16.8 (K_M = 140 μM[5])

MAO A···WT: −17.0

MAO A···SA: −15.8

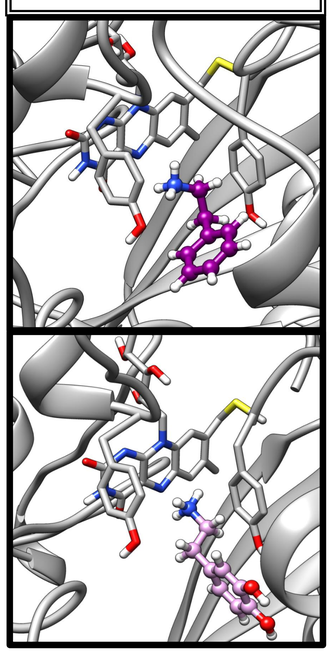
serotonin

−20.1 (K_M = 137 μM[5])

MAO A···WT: −15.5

MAO A···SA: −23.0

MAO B



phenylethylamine

−12.0 (K_M = 4 μM[5])

MAO B···WT: −9.4 [−10.8]

MAO B···SA: −14.8 [−11.8]

dopamine

−20.7 (K_M = 229 μM[5])

MAO B···WT: −15.4 [−19.7]

MAO B···SA: −23.0 [−15.6]

CONCLUSION

A combination of docking and MD simulations reveals the spike protein from WT and SA SARS-CoV-2 variants possesses affinity towards the MAO enzymes comparable to that for its ACE2 receptor. Our results also show that formed complexes significantly lower MAO affinities towards their neurotransmitters in the WT infection, while a more severe SA strain has an opposite effect. Knowing that alterations in MAO substrate levels are a potential foundation of oxidative stress and various disorders, such as Parkinson's or Alzheimer's disease, the demonstrated feasibility of the spike···MAO complex formation opens a possibility that the interference with the brain MAO activity is responsible for an increased development and faster progression of neurodegenerative illnesses in COVID-19 infected individuals.

međunarodni znanstveno-stručni skup
19. Ružičkini dani
DANAS ZNANOST – SUTRA INDUSTRIJA
21. – 23. rujna 2022. | Vukovar, Hrvatska

REFERENCES
[1] Y. Wu, X. Xu, Z. Chen, J. Duan, K. Hashimoto, L. Yang, C. Liu, C. Yanga, *Brain. Behav. Immun.* **2020**, *87*, 18–22.
[2] M. Taquet, J. R. Geddes, M. Husain, S. Luciano, P. J. Harrison, *Lancet Psychiatry* **2021**, *8*, 416–427.
[3] L. Hok, H. Rimac, J. Mavri, R. Vianello, *Comput. Struct. Biotechnol. J.* **2022**, *20*, 1254–1263.
[4] M. Cuperlovic-Culf, E. L. Cunningham, H. Teimoorinia et al., *Sci. Rep.* **2021**, *11*, 10629.
[5] M. B. H. Youdim, D. Edmondson, K. F. Tipton, *Nat. Rev. Neurosci.* **2006**, *7*, 295–309.
FUNDING: CAT PHARMA Project (KK.01.1.1.04.0013) and Slovenian Research Agency (P1-0012)

EUROPSKA UNIJA ZAJEDNO DO FONDOVA EU
Operativni program KONKURENTNOST I KOHEZIJA
EUROPSKI STRUKTURNI I INVESTICIJSKI FONDOVI
arrs SLOVENIAN RESEARCH AGENCY