



Comment

# Comment on Kopańska et al. Disorders of the Cholinergic System in COVID-19 Era—A Review of the Latest Research. *Int. J. Mol. Sci.* 2022, 23, 672

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We read the recent review article by Marta Kopańska et al. titled “the Disorders of the Cholinergic System in COVID-19 Era—A Review of the Latest Research” [1]. First of all, we would like to congratulate the authors for the accurate revision of literature about COVID-19 and the cholinergic system [1]. The authors focused on the impairments of the cholinergic system, reporting evidence of dysregulation in acetylcholine (ACh)/acetylcholinesterase (AChE) activities and alteration in ACE2 circulating levels, as observed in myasthenia gravis, ocular myasthenia gravis, noxious skeletal muscles and multisystem inflammatory syndrome [1]. In this context, we would point out a few recent publications that might provide additional value to this interesting revision of the literature.

First, the author stated that “The SARS-CoV-2 spike protein has a sequence like neurotoxins, capable of binding nicotinic acetylcholine receptors (nAChR). This may be proof that SARS-CoV-2 can bind nAChR” [1]. The authors referred to the studies from Farsalinos and coworkers on the presence of a region of homology between neurotoxin and SARS-CoV-2 sequences [2]. We recently explored this aspect by confirming this homology and showing additional regions of homology between neurotoxin and SARS-CoV-2 sequences, which are adjacent to those previously reported [3]. Subsequently, we extended the analysis to the presence of different affinity regions and hypothesized that the RNA polymerase might be directly involved in this production, as we mentioned a “jumping mechanism” inside the last ORF of viral genome for spike glycoprotein, an aspect common to other viruses [3–5]. Due to this 50–60% homology with conotoxins, these small peptides might be responsible for the clinical manifestations (neurological, hemorrhagic and thrombotic) observed in COVID-19 patients [3,6–10]. This point has been recently sustained by the presence of circulating and local toxic products [3,9,10].

Second, the authors stated “there are many promising therapies that will prevent the SARS-CoV-2 virus from binding to the nicotinic receptor,” implying the possibility of new and attractive therapeutic and perhaps preventive implications [1,9,10]. To those therapies targeting the cholinergic system, we would point out the observations that elderly subjects develop more severe forms of disease or the worsening of disease in some youngsters [2,3]. Changes in microbiota upon aging or the presence of dysbiosis and/or certain tissue restricted bacterial profiles might account at least in part for these observations [11–17]. A correlation between specific nasopharyngeal/gut microbiota and disease severity has been

previously reported, implying a probable participation of mucosal microbiota (nose, gut, conjunctiva) in some COVID-19 manifestations [11–13]. These observations encourage the latest hypothesis on the “bacteriophage-like” behavior of SARS-CoV-2 [14,18,19].

Overall, it is noteworthy to mention that multiple cholinergic receptors (cholinergic innervation) are expressed by ocular tissues [6]. As we cannot exclude that SARS-CoV-2 virus can also take advantage of the eye to enter the body, as ACE-2 receptors are expressed by mucosal conjunctiva as well as by some retinal subpopulations, and due to a peculiar microbiota populating the ocular surface, it is of great interest to highlight another article reporting that the omicron variant can bind ACE-2 receptors better than the Beta and Delta variants. This aspect would support higher diffusion and, in particular, more incidents of conjunctivitis, which be of some interest in any attempt to control the spread of the disease [7,8].

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