EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

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Please cite this article as: Leung JM, Yang CX, Sin DD. COVID-19 and Nicotine as a Mediator of ACE-2. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.01261-2020).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

COVID-19 and Nicotine as a Mediator of ACE-2

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We recently reported that current smokers and those with COPD had higher airway epithelial cell expression of the angiotensin-converting enzyme-2 (ACE-2) viral entry receptor [1]. We thus read with great interest the work of Russo *et al.* [2] which proposes a mechanism for this finding, namely that this upregulation is mediated by nicotine exposure specifically through the α7 subtype of nicotine acetylcholine receptors (α7-nAChR). While exposure to increasing concentrations of nicotine caused epithelial cells to increase ACE-2 levels, subsequent gene silencing of α7-nAChR appeared to significantly dampen this response. A secondary transcriptome sequencing analysis of our cohort (consisting of 42 subjects who underwent bronchoscopy for epithelial cell brushings [1]) reveals evidence in support of this hypothesis. We found that airway epithelial cell expression of *CHRNA7*, encoding α7-nAChR, was significantly correlated with the expression of *ACE2* (**Figure 1**, Pearson $r=0.54$, $p=2.31 \times 10^{-8}$). There was significantly higher *CHRNA7* expression in those with COPD (2.75 ± 0.73 vs. 2.14 ± 0.43 in those without COPD, $p=1.47 \times 10^{-4}$), with a trend towards higher expression in current smokers compared to former and never smokers (2.86 ± 0.92 in current smokers, 2.35 ± 0.57 in former smokers, and 2.27 ± 0.45 in never smokers, $p=6.16 \times 10^{-2}$). *CHRNA7* was also negatively correlated with forced expiratory volume in 1 second percent predicted (Pearson $r=-0.37$, $p=2.83 \times 10^{-4}$). Interestingly, *CHRNA7* was positively if weakly correlated with body mass index (Pearson $r=0.14$, $p=6.31 \times 10^{-3}$), raising the intriguing possibility that nicotine receptor mediation of ACE-2 may also be related to why obese individuals have made up a considerable proportion of COVID-19 cases [3].

Together, these data further help to characterize the connections between airway epithelial ACE-2, α7-nAChR, and the unique vulnerability of patients with COPD to severe COVID-19. α7-nAChR's widespread abundance in the human body, from neuronal tissue to immune cells to the lung and digestive tract, and its various roles in diseases such as schizophrenia [4], Alzheimer's disease [5],

and Parkinson's disease [6] has meant that considerable work has already been done to target α7-nAChR as a therapeutic modality. As an example, α7-nAChR antagonists for the purpose of smoking cessation have long been proposed [7] and the idea of potentially repurposing these compounds for a pandemic with few therapeutic options currently available is certainly appealing. Whether α7-nAChR-selective antagonists such as methyllycaconitine [8] and α-conotoxin [9] can meaningfully alter ACE-2 expression to prevent SARS-CoV-2 entry into the airway epithelium seems the next logical investigation in our furious pursuit for better therapeutics.

References

1. Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, Dorscheid DR, Sin DD. ACE-2 Expression in the Small Airway Epithelia of Smokers and COPD Patients: Implications for COVID-19. *Eur Respir J* 2020.
2. Russo P, Bonassi S, Giacconi R, Malavolta M, Tomino C, Maggi F. COVID-19 and smoking: is nicotine the hidden link? *Eur Respir J* 2020.
3. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, Prill M, Chai SJ, Kirley PD, Alden NB, Kawasaki B, Yousey-Hindes K, Niccolai L, Anderson EJ, Openo KP, Weigel A, Monroe ML, Ryan P, Henderson J, Kim S, Como-Sabetti K, Lynfield R, Sosin D, Torres S, Muse A, Bennett NM, Billing L, Sutton M, West N, Schaffner W, Talbot HK, Aquino C, George A, Budd A, Brammer L, Langley G, Hall AJ, Fry A. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep* 2020: 69(15): 458-464.
4. Freedman R, Leonard S, Gault JM, Hopkins J, Cloninger CR, Kaufmann CA, Tsuang MT, Farone SV, Malaspina D, Svrakic DM, Sanders A, Gejman P. Linkage disequilibrium for schizophrenia at the chromosome 15q13-14 locus of the alpha7-nicotinic acetylcholine receptor subunit gene (CHRNA7). *Am J Med Genet* 2001: 105(1): 20-22.
5. Guan ZZ, Zhang X, Ravid R, Nordberg A. Decreased protein levels of nicotinic receptor subunits in the hippocampus and temporal cortex of patients with Alzheimer's disease. *J Neurochem* 2000: 74(1): 237-243.
6. Banerjee C, Nyengaard JR, Wevers A, de Vos RA, Jansen Steur EN, Lindstrom J, Pilz K, Nowacki S, Bloch W, Schroder H. Cellular expression of alpha7 nicotinic acetylcholine receptor protein in the temporal cortex in Alzheimer's and Parkinson's disease--a stereological approach. *Neurobiol Dis* 2000: 7(6 Pt B): 666-672.
7. Ramachandran Nair L, Liu X. Targeting the alpha4beta2- and alpha7-Subtypes of Nicotinic Acetylcholine Receptors for Smoking Cessation Medication Development. *J Addict Res Ther* 2019: 10(2).
8. Panagis G, Kastellakis A, Spyraki C, Nomikos G. Effects of methyllycaconitine (MLA), an alpha 7 nicotinic receptor antagonist, on nicotine- and cocaine-induced potentiation of brain stimulation reward. *Psychopharmacology (Berl)* 2000: 149(4): 388-396.
9. Liang J, Tae HS, Xu X, Jiang T, Adams DJ, Yu R. Dimerization of alpha-Conotoxins as a Strategy to Enhance the Inhibition of the Human alpha7 and alpha9alpha10 Nicotinic Acetylcholine Receptors. *J Med Chem* 2020: 63(6): 2974-2985.

Figure 1. Transcriptome profiles generated through RNA-Seq of airway epithelial cells demonstrated a significant positive correlation between *ACE2* and *CHRNA7* expression.