RESPONSE TO LETTER TO THE EDITOR

Response to Comments on “Does COVID19 Infect the Brain? If So, Smokers Might Be at a Higher Risk”

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We thank the correspondent for his reading and comments [Speth, 2020] on our Perspective article “Does COVID19 infect that brain? If so, smoker’s might be at a higher risk”, which examines interactions between smoking and COVID19. This article was among the first to explore relations between smoking and possible brain infection of SARS-CoV2. Citing earlier findings on the pathology of coronaviruses and the actions of nicotine within the brain and RAS, we hypothesized neurologic complications during COVID19 and suggested a receptor-driven mechanism of risk in smokers. As pointed out by the correspondent, this Perspective followed an earlier article by us on smoking’s role in cardiopulmonary vulnerability during COVID19 (Olds and Kabbani, 2020). Thus, the Perspective extends ideas on mechanisms of susceptibility driven by nicotine on viral infection in neural cells based on published evidence of interactions between the nicotinic acetylcholine receptor (nAChR) and the viral target protein, angiotensin converting enzyme 2 (ACE2). Before addressing the correspondent’s comments however, we would like to note that since our article was accepted in March, published findings by various laboratories have supported our hypothesis that nicotine use is an important health factor in COVID19 and that neural complications occur in a noticeable number of infected individuals (reviewed in Ellul et al., 2020). Recent evidence also underscores our proposed mechanism for nicotine mediated upregulation of ACE2 as a possible driver for COVID19 complications (e.g., Cai et al., 2020; Smith et al., 2020; Leung et al., 2020). Nicotine signaling through the nAChR during SARS-CoV2 infection is now an important area of research with therapeutic potential.

The correspondent raises several points that implicitly misstate the premise and in some cases the content of our Perspective. In a broad response to the critique we would like to point out that his statement “ACE2 is an extremely well characterized protein” is in our view misleading for efforts to gain knowledge on the pathology of the SARS-CoV2 coronavirus. In our Perspective and here again we suggest the existence of compelling evidence for interactions between nAChRs and ACE2 important for RAS-dependent and -independent signaling within cells. As discussed in our Perspective, a profile of the ACE2 transcript within the adult human brain suggests a role for cholinergic transmission in SARS-CoV2 neuroinfection in various regions.

While it is correct that a subset of studies cited by the correspondent and referenced by us in the Perspective show

that nicotine treatment can *decrease* in ACE2 levels (e.g., Ferrari et al., 2008), additional work cited in our Perspective indicates that nicotine *increases* ACE2 expression in humans. In fact, even as we agree with the correspondent’s assertion, our hypothesis extends evidence from recent findings and takes into account data from human samples and rodent models where smoking and nicotine can *increase ACE2 expression* in tissue as the lungs and brain (Cai, 2020a,b; Cai et al., 2020 Preprint; Smith et al., 2020; Choi et al., 2020). Conflicting results on ACE2 in the literature may reflect a species related regulation of ACE2 at the gene or transcript level. For example, it is possible that nicotine can modulate ACE2 differently between humans and mice and between different tissue types due to the expression of different nAChR subunits. Such factors are important and should be examined carefully in the context of research on SARS-CoV2 using animal models and cell systems.

In disagreement with the correspondent’s statement “while there is little doubt that smoking nicotine-containing tobacco products predisposes smokers to increased disease susceptibility, this predisposition arises from adverse effects of nicotine on the cardiovascular system”, we do not dismiss the established impact of nicotine on key SARS-CoV2 target organs such as the brain and the immune system for several reasons. First, nAChRs are abundant in neural tissue and a wide range of neurologic symptoms, from anosmia to mental confusion and memory loss, are reported symptoms of COVID19. As stated in our Perspective, the virus could infect brain regions such as the striatum and cortex based on the profile of ACE2 expression in the human adult brain. In such a scenario, the impact of smoking on the activity and expression of nAChRs in such regions can render smokers at a higher risk for COVID19 complications through nAChR mediated ACE2 signaling.

Secondly, nAChRs are in immune cells and signaling through receptors such as the $\alpha 7$ nAChR can reduce inflammation through TNF α release (King et al., 2017). Thus nicotine’s actions on the immune system are important for COVID19 and may directly contribute to a dampening of inflammatory responses such as the “cytokine storm”. In this regard, anti-inflammatory signaling by the nAChR may account for lowered hospitalization in a subset of COVID19 individuals with a smoking history (Farsalinos et al., 2020). Alternatively, smoking may lead to a heightened risk in other

individuals with smoking history due to an *increase* in brain ACE2 expression (Choi et al., 2020).

Lastly, we find the statement by the correspondent “the premise of the commentary is that there was a “linking increased brain susceptibility to SARS-CoV-2 infection with smoking “...based upon known functional interactions between the nicotinic receptor and ACE2.” to be a misconstruction of the Perspective, which clearly states otherwise: “*Here, we raise the question of nicotine-associated comorbidity to COVID19 in the context of the brain based on published evidence that the viral target receptor ACE2 is expressed in the brain and functionally interacts with nAChRs....we suggest that were COVID19 to breach the blood brain barrier (as evidence suggests for SARS) during the course of ongoing infection, interactions with ACE2 in multiple brain regions would present the virus the opportunity to infect the brain of COVID19 patients*”

We conclude by challenging the premise of the correspondent’s critique based on the notion that knowledge of ACE2 resides within a classic RAS system. Instead we advocate for a bold and thorough scientific view of how and where the SARS-CoV2 operates *vis a vis* interactions with ACE2 in various organ systems. Now more than ever it is important to embrace efforts and ideas that cross domains to gain an understanding and a path toward treatment.

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