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Ⓞ Olfactory Nasal Nitric Oxide Link in COVID-19: A Marker of Neurogenesis or Risk Factor for Chronic Rhinosinusitis?

To the Editor:

I read with interest the article by Hua-Huy and colleagues (1) describing an important finding of significantly raised levels of nasal nitric oxide (NO) during the recovery phase (≥ 6 wk to 5

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mo) after complete resolution of coronavirus disease (COVID-19)-related anosmia (1). Interestingly, the nasal NO levels were significantly greater in patients with COVID-19 who developed anosmia than those who had preserved olfaction (1). I believe the authors observations are of great clinicopathological significance to understand the process of COVID-19-induced anosmia and its recovery, but the findings may not signify persistent inflammation or risk for progression to chronic rhinosinusitis disease (CRS).

Lower levels of nasal NO have been consistently found in patients with CRS; nasal NO levels are inversely related with the rhinosinusitis disability index (2). Conversely, increasing levels of nasal NO are often considered as a marker of recovery from CRS and success of treatment (2). Therefore, the higher measured levels of nasal NO observed in COVID-19 following recovery of anosmia (1) should not be considered as a risk factor for progression to CRS; instead, it appears to correlate with the process of recovery of olfaction. I, herein, propose an alternate hypothesis for the authors' findings that can better explain the clinical pathophysiology of COVID-19-associated anosmia.

During the early phase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of sustentacular cells and ciliated nasal epithelial cells, most individuals possibly develop effective innate immune responses in the nasal epithelium with limited infectivity of the lower airways and milder disease (3). However, the IFNs, so produced, can induce the expression of indoleamine 2,3-dioxygenase (IDO) activity on the nasal epithelial and endothelial cells, without widespread epithelial cell damage (4, 5). As a result, in SARS-CoV-2 infection, the tryptophan catabolism in the nasal epithelium may be diverted toward kynurenine pathways. The finding that Influenza A virus induces IDO expression, resulting in tryptophan depletion and rise in kynurenine levels in nasal epithelial cells after infection in air-liquid interface model, supports the above arguments (6). Interestingly, SARS-CoV-2 infection is associated with increased levels of neurotoxic metabolites with glutaminergic activity: 3-hydroxykynurenine (3-HK), quinolinic acid (QA), and anthranilic acid; however, the neuroprotective by-products such as kynurenic acid and xanthurenic acid that possess glutamate antagonistic and α -7 nicotinic receptor inhibitory actions are decreased (7). I believe that from the olfactory epithelium, the locally generated 3-HK and QA reach the olfactory bulb (OB) via the transmucosal route. As the olfactory epithelium and OB neurons have high *N*-methyl *D*-aspartate receptor expression (8), 3-HK and QA can induce direct neuronal injury resulting in anosmia (Figures 1A and 1B). Interestingly, bilateral administration of glutamate agonist, *N*-methyl *D*-aspartate, in the OB induces olfactory dysfunction by direct neurotoxicity with a spontaneous recovery 2 weeks after excitotoxicity lesion of the OBs (8). This characteristically correlates with the duration of anosmia in patients with COVID-19 (1). Importantly, elevated IDO activity inhibits NOS (NO synthase) and vice versa (9). Thus, recovery of smell in patients with COVID-19 may be due to the resolution of elevated IDO expression and concurrent increases in NO production (Figure 1C).

Based on the above arguments, I propose that the local nasal inflammation in the early phase of SARS-CoV-2 infection results in an injury to the olfactory neurons with concurrent decrease in nasal NO levels. However, from the evidence that, irrespective of the

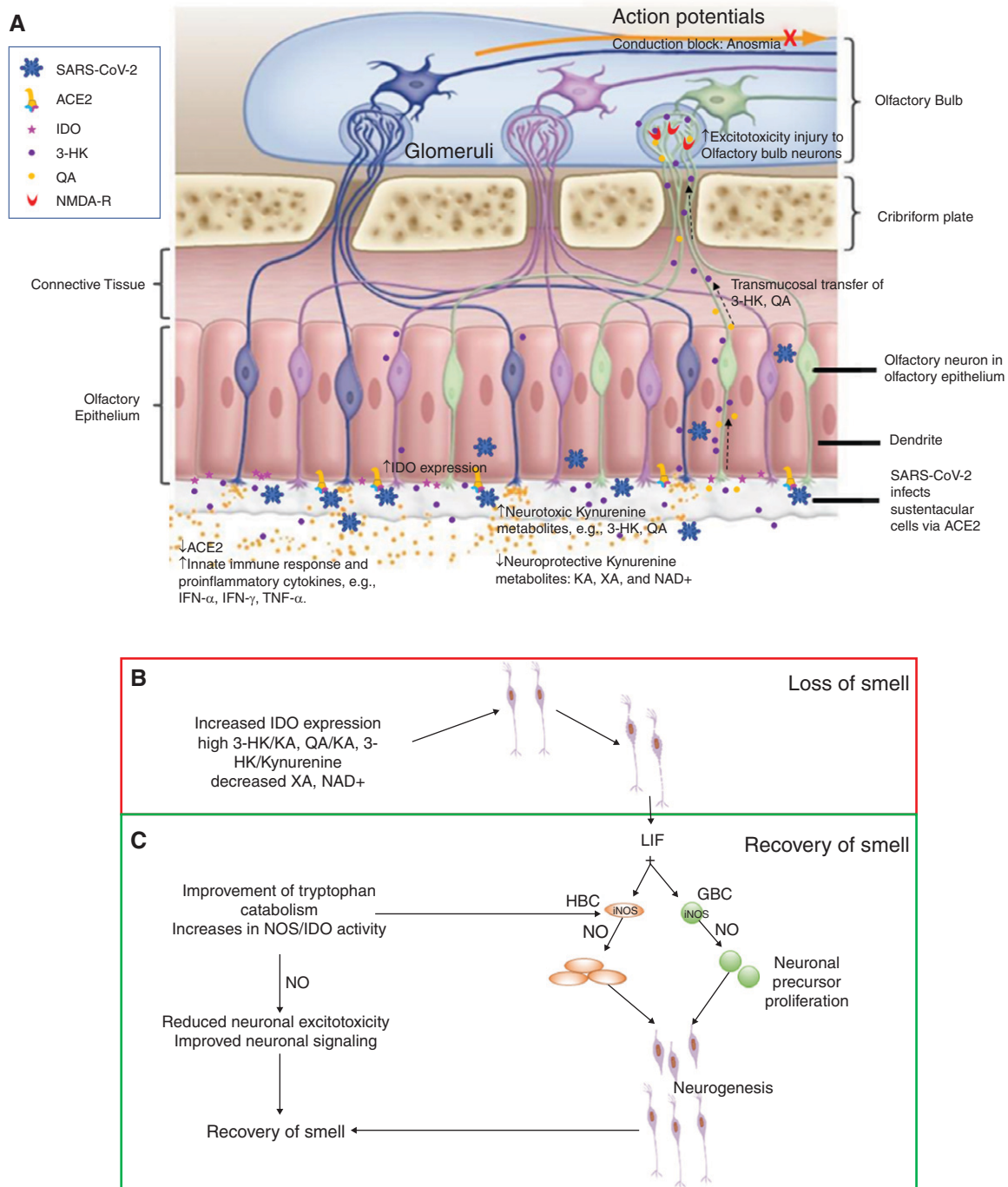


Figure 1. (A and B) Schematic representation of the mechanisms of anosmia in coronavirus disease (COVID-19). (C) Mechanisms linking increase in nasal nitric oxide levels with neurogenesis and recovery of smell in COVID-19. 3-HK = 3-hydroxykynurenine; ACE2 = angiotensin converting enzyme 2; GBC = global basal cell; HBC = horizontal basal cell; IDO = indoleamine 2,3-dioxygenase; iNOS = inducible nitric oxide synthase; KA = kynurenic acid; LIF = leukemia inhibitory factor; NAD = nicotinamide adenine dinucleotide; NMDA-R = *N*-methyl *D*-aspartate; NO = nitric oxide; NOS = nitric oxide synthase; QA = quinolinic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNF- α = tumor necrosis factor α ; XA = xanthurenic acid.

etiology (inflammatory or noninflammatory), the nasal NO levels decrease in patients with decreased sense of smell (10), one can conclude that the lower nasal NO levels in patients with olfactory loss are more closely linked to the injury of olfactory sensory neurons

rather than inflammation alone. Nonetheless, the recovery of smell loss is associated with the process of neurogenesis that involves an increase in the expression of inducible NOS in the basal progenitor cells secondary to the stimulation by leukemia inhibitory factor

released from the injured neurons (11) (Figure 1C). The increase in nasal NO levels during the recovery phase from rhinitis-induced inflammation and anosmia is already well evident (2); I believe this can secondarily be due to the normalization of tryptophan catabolism. Overall, the high nasal NO levels should not be considered as a simple marker of persistent inflammation and a risk factor for CRS in patients recovering from COVID-19-induced anosmia.

In conclusion, the proposed hypothesis explains why patients with COVID-19 with anosmia develop less severe disease than those with preserved olfaction and why higher nasal NO levels were evident in patients with COVID-19 after recovery of anosmia (1). I believe measuring the levels of nasal NO in patients with COVID-19 during the acute phase of anosmia and in patients with postacute COVID-19 syndrome with persistent anosmia could provide further understanding about the olfactory–nasal NO link in COVID-19. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Jain

From the Authors:

We thank Dr. Amit Jain for his interesting hypothetical explanation of the persistently high levels of nasal nitric oxide (NO) in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and having coronavirus disease (COVID-19)-associated anosmia as compared with patients without anosmia (1). We agree with Dr. Jain that IFN-induced increase of indoleamine 2,3-dioxygenase (IDO) activity can divert tryptophan catabolism toward the kynurenine pathways in the nasal epithelium. We also concur that the resulting rise in 3-hydroxykynurenine levels could directly cause neuronal injury leading to anosmia in some patients with COVID-19. As increased IDO activity may adversely affect NO synthesis (2), Dr. Jain has proposed an alternate explanation suggesting that nasal NO is reduced during the acute phase of anosmia, and its high levels evidenced in our study (1) could be viewed as a sign of recovery from the initial neuronal injury rather than a biological proof of persistent inflammation.

Although we fully acknowledge the plausibility of Dr. Jain's interesting hypothesis, we also would like to seize this opportunity to broaden the discussion to another key player of the NO pathways, namely, the neuronal NO synthase (NOS). The gas NO stemming from the upper airways can be synthesized from three different NOS isoforms, that is, the inducible, endothelial, and neuronal NOS (3). Although inducible NOS plays a pivotal role in innate and adaptive immunity (4), neuronal NOS localized in the upper airways critically regulates NO levels to maintain normal cilia (5) and olfactory (6) functions in humans. All three NOS isoforms are highly regulated heme-thiolate proteins (7) whose enzymatic activities can be inhibited by large amounts of NO acting as a negative feedback loop on NO synthesis (8). One possible alternate explanation for our findings of high levels of nasal NO 5 months after acute anosmia (1) could be the differential implications of inducible and neuronal NOS over the time course of SARS-CoV-2 infection. During the acute phase, activation of the inducible NOS would lead to marked increase in NO synthesis, which, in turn, inhibits neuronal NOS activity and causes anosmia. Inhibition of neuronal NOS progressively wears off with reduced activity of inducible NOS, enabling olfaction

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