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COVID-19, perioperative neurocognitive disorder and SARS-CoV-2-induced dysregulation of the renin–angiotensin system and kynurenine metabolism. Comment on *Br J Anaesth* 2021; 127: e113–e115

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Editor—Wei and colleagues[1] postulated COVID-19 as a risk factor for perioperative neurocognitive disorders (PNDs). We agree that older individuals experiencing COVID-19 are at special risk, but believe that the proposed mechanisms are incomplete.

The authors offered SARS-CoV-2 invasion into the CNS as a mechanism.[1] However, there is limited evidence of SARS-CoV-2 infection of neurones, and brain autopsies of patients with COVID-19 show no neuronal infection.[2] Direct viral involvement of brain or olfactory nerves was limited to detecting low levels of viral RNA and rare viral antigens in cranial nerves and scattered brainstem cells[3,4]; the presence of CNS SARS-CoV-2 was not associated with neuropathological severity.[4] Although translational research supports spike-protein-mediated direct injury of the blood-brain barrier (BBB) without evidence of neuronal infection,[5] immunohistochemistry using antibodies that recognise the viral spike protein, has been negative in most human cases.[3] Hence, it is important to consider pathological processes distinct from virus or virus-related proteins related to SARS-CoV-2 infection in inducing indirectly BBB injury and neuroinflammation. These have also been associated with Alzheimer's disease (AD) and PND.[6]

Based on the finding of increased angiotensin-converting enzyme 2 (ACE2) expression in AD brain,[7] Wei and colleagues[1] considered patients with AD to have greater risk for SARS-CoV-2-induced CNS infection. However, this is arguable, as the structure and function of ACE2 isoforms upregulated during inflammation are unclear. Recent studies show that interferons and viruses induce ACE2 isoforms that lack angiotensin-II (Ang-II) catalytic activity and differ from full-length SARS-CoV-2 receptors.[8,9] Thus, it is unclear whether interferon-gamma (INF-γ)-induced upregulation of ACE2 as evident in SARS-CoV-2 infection,[10] and possibly in other inflammatory situations, such as AD,[1,7] increases susceptibility to SARS-CoV-2 infection.

Ding and colleagues[7] found no relationship between ACE2 upregulation and AD severity, whilst elsewhere ACE2 downregulation in brain correlated with increased expression of amyloid beta (Aβ), tau pathology, AD disease progression, and

worsened outcomes.[11] Downregulation of normal ACE2 and increased expression of ACE2 isoforms lacking catalytic activity could establish hyperactive angiotensin-converting enzyme (ACE)–Ang-II–angiotensin 1 receptor (AT1R) signalling in AD[11] and COVID-19.[12]

To implement preoperative strategies to alleviate neurological consequences of COVID-19, one must propose pathophysiological models that link COVID-19 with AD and PND.[6] We postulate two such pathways that may be triggered by SARS-CoV-2-induced epithelial–endothelial cross-talk[12] and inflammation (Fig. 1).

Renin–angiotensin system

SARS-CoV-2 infection in nasal and olfactory epithelium produces ACE2 downregulation with upregulation of proinflammatory cytokines, establishing high local expression of ACE and Ang-II.[12] From the olfactory epithelium, Ang-II can diffuse transmucosally to produce high concentrations in the olfactory bulb, prefrontal cortex, and hippocampus[13]; these are brain regions with high expression of AT1Rs.[14] Hence, high Ang-II-mediated activity in SARS-CoV-2 could be a mechanism for hippocampal neurotoxicity. Importantly, increased central Ang-II induces amyloidogenesis during stress, and Aβ production is completely abolished by intracerebroventricular administration of losartan.[15] Similarly, AT1R deficiency decreased Aβ amyloid and amyloid plaque formation in a mouse model of AD.[16]

Angiotensin-III, a metabolite of Ang-II, is associated with Aβ and tau pathology.[17] Increased ACE activity in medial hippocampus, parahippocampal gyrus, frontal cortex, and caudate nucleus correlates with Aβ plaque load.[18] The ACE/ACE2 ratio increases, whilst a decrease in the Ang-II/Ang (1–7) ratio occurs in AD[11] and possibly in the pathogenesis of COVID-19.[12] In fact, centrally acting ACE inhibitors reduce dementia and cognitive decline, and enhance memory in mild-to-moderate AD,[19] and candesartan, an AT1R antagonist, diminishes the incidence of non-fatal stroke.[19]

Increased hippocampal expression of Ang-II and AT1R is linked with hippocampal BBB disruption as early as 6 h after surgery in aged rats, whereas AT1R antagonists restore BBB integrity by suppressing the canonical surgery-induced nuclear factor-κB activation cascade.[20] Importantly, starting ACE
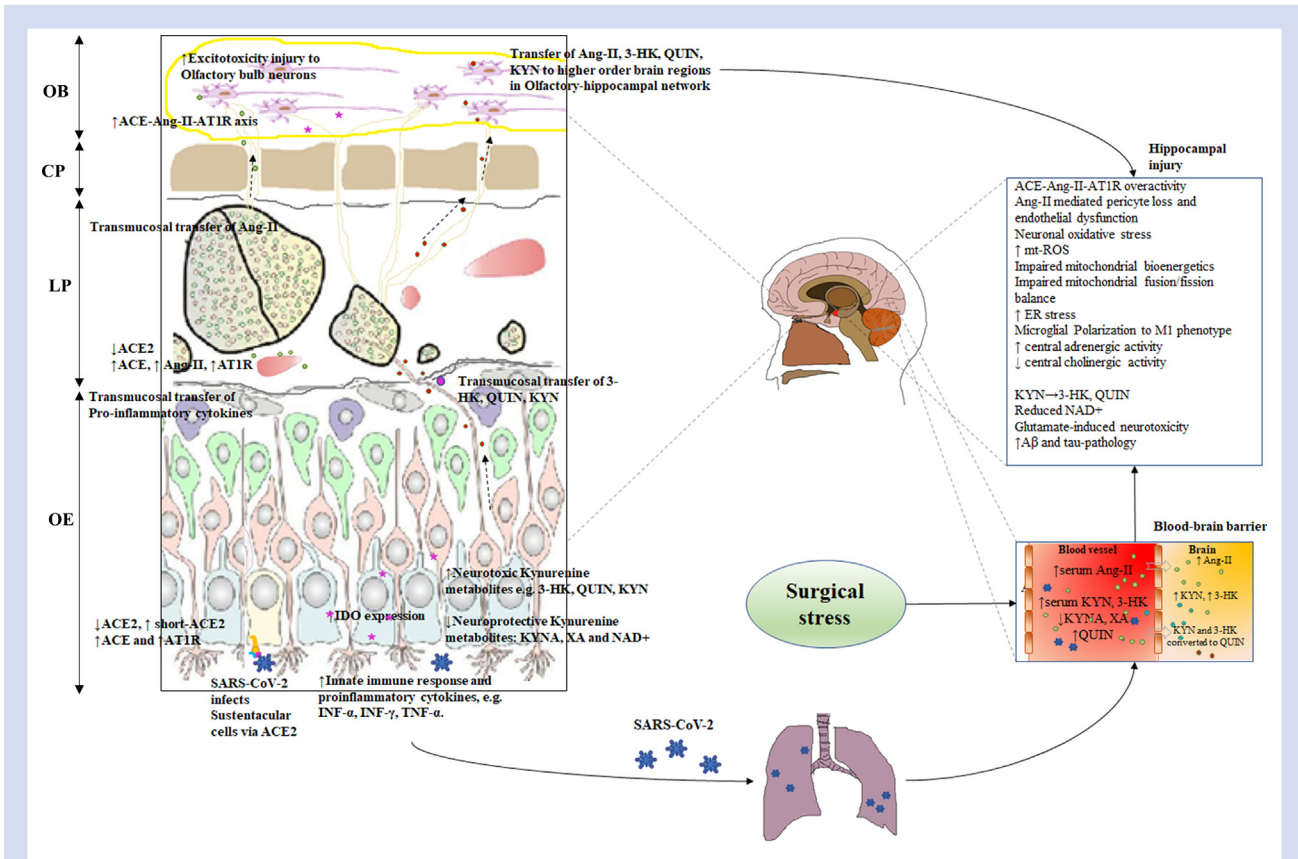
Fig 1. Mechanism of dysregulated renin—angiotensin system and kynurenine metabolism-mediated SARS-CoV-2-induced neurotoxicity and the potential association between SARS-CoV-2 infection, surgical stress, and perioperative neurocognitive dysfunction in cognitive impairment. SARS-CoV-2 infection of the nasal epithelial cells and olfactory sustentacular cells is associated with downregulation of ACE2 and release of pro-inflammatory cytokines and interferon in the nasal and olfactory epithelium. This results in upregulation of indole-amine 2,3-dioxygenase activity, ACE/ACE2 imbalance, increased expression of AT1R, and high local concentration of Ang-II, KYN, 3-HK, and QUIN. Transmucosal transport of these pro-inflammatory and neurotoxic mediators to the olfactory bulb results in excitotoxic neuronal injury and anosmia. Direct transfer to Ang-II, KYN, 3-HK, and QUIN to the hippocampus via olfactory—hippocampal pathways is an early mechanism. COVID-19 pneumonia results in high systemic levels of serum Ang-II, KYN, 3-HK, and QUIN, whilst the levels of tryptophan, KYNA, and XA are reduced. Surgical stress induces systemic inflammation, increases systemic Ang-II, and aggravates deregulated KYN metabolism. Circulating Ang-II directly acts on the circumventricular organs, including hippocampus, and induces BBB permeability by promoting endothelial dysfunction. Circulating KYN and 3-HK cross the BBB to contribute directly to the cerebral pools and are further metabolised intracerebrally to QUIN. Circulating QUIN, KYNA, and XA cross the BBB poorly under normal conditions. SARS-CoV-2 neuroinvasion via retrograde axonal route from the olfactory epithelium or haematogenous spread through BBB remains an insignificant feature. High CNS pool of Ang-II, 3-HK, QUIN, and KYN induces hippocampal injury by aggravating neuroinflammation, excess mtROS, and Aβ accumulation. ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Ang-II, angiotensin II; AT1R, angiotensin 1 receptor; Aβ, amyloid beta; BBB, blood—brain barrier; CP, cribriform plate; ER, endoplasmic reticulum; IDO, indole-amine 2,3-dioxygenase; INF-α, interferon alpha; INF-γ, interferon gamma; KYN, kynurenine; KYNA, kynurenic acid; LP, lamina propria; mtROS, mitochondrial radical oxygen species; NAD+, nicotinamide adenine dinucleotide plus; OB, olfactory bulb; OE, olfactory epithelium; PND, perioperative neurocognitive disorder; QUIN, quinolinic acid; RAS, renin—angiotensin system; TNF-α, tumour necrosis factor alpha; XA, xanthurenic acid; 3-HK, 3-hydroxykynurenine.

inhibitors or AT1R blockers in the early postoperative period was associated with reduced delirium in critical care settings.[19]

Tryptophan—kynurenine metabolism

Interferon-γ and Ang-II via INF-γ induce indoleamine 2,3-dioxygenase (IDO) activity after SARS-CoV-2 infection.[21] Increased expression of IDO activity and kynurenine (KYN)/tryptophan (TRP) ratio is evident in nasal epithelium after influenza type A infection.[22] Altered KYN metabolism is an early marker of inflammation in SARS-CoV-2 infection, high levels of neurotoxic metabolites (3-hydroxykynurenine [3-HK] and quinolinic acid [QUIN]) with low levels of neuroprotective by-products (kynurenic acid [KYNA]). The xanthurenic acid (XA) of KYN pathways is linked with COVID-19 severity.[21] In fact, high 3-HK/KYN, 3HK/KYNA, and QUIN/KYNA ratios are evident on metabolomic studies in COVID-19.[21] High levels of neoptrin and low levels of XA are additional markers of severity.[21] Severe COVID-19 is associated with reduced

quinolinic acid phosphoribosyltransferase expression and reduced production of nicotinamide adenine dinucleotide.[23] 3-HK and QUIN are strong competitive agonists of glutamate.[24] Contrarily, both KYNA and XA inhibit N-methyl-D-aspartate receptors. KYNA also inhibits presynaptic α7 nicotinic receptors in hippocampal neurones, but increases non-α7 nicotinic receptor expression.[24] 3-HK may cause reactive oxygen species formation leading to microvascular damage, increased BBB permeability, and neurotoxicity. Increased QUIN and 3-HK levels in astrocytes and neurones result from cytokines, such as INF-γ, tumour necrosis factor-α, and interleukin-1β.[24] Increased QUIN and 3-HK levels can cause nerve conduction abnormalities and neurological toxicity especially in the hippocampus, striatum, and other parts of the neocortex that are sensitive to QUIN.[24]

We hypothesise that SARS-CoV-2 infection produces QUIN and 3-HK from olfactory epithelium that diffuses transmucosally to produce direct neuroexcitatory injury to olfactory bulb neurones, resulting in anosmia. Interestingly, direct glutamate administration at the level of olfactory bulb induces anosmia that recovers spontaneously within 2 weeks,[25] the duration of anosmia usually seen in COVID-19.[26] Transmucosal spread of KYN metabolites to higher-order brain structures in the olfactory—hippocampal pathway is a possibility. Systemic KYN metabolites, KYN and 3-HK, in contrast to plasma KYNA, can readily cross the BBB to generate high central QUIN levels and induce neuronal inflammation, oxidative stress, and hippocampal injury.

Similar alterations in KYN metabolism are seen in patients with neurovascular diseases.[21,24] Ageing and AD are also associated with deregulated KYN metabolism. Alteration of KYN metabolism, involving tryptophan depletion along with marked increases in QUIN, but decreases in KYNA and XA plasma levels occurred in both AD and with ageing.[24]

Anaesthesia and surgery are associated with inflammatory changes and alterations in TRP oxidative metabolism, which may contribute to postoperative cognitive dysfunction.[27] Immune-mediated metabolism of KYN is involved in PND after cardiopulmonary bypass.[27]

In conclusion, dysregulated renin—angiotensin and KYN metabolism pathways in COVID-19 pathogenesis are similar to those in ageing, AD dementia, and PND. Studies confirming the role of these pathways in COVID-19 neurocognitive decline are urgently needed to establish targets for reducing PND in patients who had COVID-19 and are undergoing surgery. This is further highlighted by the evidence from the recent meta-analysis showing reduced risk of cognitive decline in older adults on AT1R blockers and ACE inhibitors with BBB-crossing potential.[28]

Declarations of interest

ML is a member of the associate editorial board of the *British Journal of Anaesthesia*. The other authors have no conflicts to declare.

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Nociception level: what's in a name?

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Editor—In our recent paper entitled 'Nociception level-guided opioid administration in radical retropubic prostatectomy: a randomised controlled trial',[1] the title was changed from 'Nociception monitor guided opioid administration in radical retropubic prostatectomy: a randomised controlled trial', during the production process, with the word 'monitor' substituted with the word 'level'. The new title may be misleading, as it may suggest that we refer to a specific proprietary monitoring system. The aim of this letter was to clarify the issue that our article title and content were generic and not specific to a specific monitoring system.

The term *nociception level* must be differentiated from any commercially available nociception monitoring index. Specifically, the term *nociception level* does not refer to the Nociception Level Index® (NOL® Index), developed by Medasense (Ramat Gan, Israel), which has been validated in several clinical nociception monitoring studies.[2] We would like to clearly state what is generic and what is product specific in the current literature.

The International Association for the Study of Pain (IASP) defines *nociception* as 'the neural process of encoding noxious stimuli'.[3] In contrast to pain, which is a subjective feeling not existing during unconsciousness, nociception still occurs during general anaesthesia.[4] According to this concept, pain cannot be measured during general anaesthesia. What can be measured during general anaesthesia are the physiological responses to nociception.[4] The IASP definition contains a note stating that, 'Consequences of encoding may be autonomic (e.g. elevated BP) or behavioural (e.g. motor withdrawal reflex or more complex nocifensive behaviour). Pain sensation is not necessarily implied'.[3]

High-potency opioids are commonly used to achieve antinociception during general anaesthesia. Other non-opioid strategies include local anaesthesia, regional anaesthesia, systemic analgesics, and anaesthetic adjuncts.[5] Nevertheless, a complete elimination of nociception during general anaesthesia is rarely achieved. Even during deep general anaesthesia, we find clear evidence for afferent signals in the CNS that do not trigger clinical responses.[6] The intensity of nociceptive signals varies substantially between individuals, but also within individuals, especially over the course of time. Patients are exposed to nociceptive stimuli of various dimensions and intensities during surgery. Therefore, the nociception/antinociception balance varies both between patients and within the same patient. In this context, the nociception level quantifies the balance between nociception and anti-nociception.