Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 CORRESPONDENCE

Anaesthesia-related drugs and SARS-CoV-2 infection

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Editor—Although there is extensive discussion of COVID anaesthesia management and infection control in the operating theatre, there are few articles examining whether perioperative anaesthesia-related drugs could affect COVID-19. Here, we discuss this possibility.

SARS-CoV-2 binding sites (Fig. 1)

Angiotensin converting enzyme 2

Angiotensin converting enzyme 2 (ACE2) is the best-known target cell receptor for SARS-CoV-2 internalisation. It is widely distributed in human cells and tissues and highly expressed in the small intestine, testes, kidneys, heart, thyroid, lungs, salivary glands, and adipose tissues, but not in the vocal folds, epiglottis, and trachea.[1]

Sigma-1 receptor

SARS-CoV-2 interacts with sigma receptors via non-structural protein 6 and coronavirus open reading frame (Orf) 9c proteins to infect cells.[2] Knockout and knockdown of sigma-1 receptor (Sig-1R), but not of Sig-2R, decreased SARS-CoV-2 replication. Modulation of Sig-1R may thus affect the early steps of viral endocytosis to change SARS-CoV-2 infection for immunologic enhancement.[3]

Famotidine and proton pump inhibitors

Famotidine is used for prophylaxis for stress ulcers in the ICU and for aspiration pneumonia as an anaesthetic premedication. A recent report[4] suggests that famotidine may improve outcome in COVID-19 patients. Histamine H_2 antagonists may activate the innate immune system to increase the count and bactericidal actions of neutrophils, enhance phagocytosis, and decrease adhesion and peroxide production. H_2 antagonists also increase natural killer cell count and cytotoxicity, enhance production of interleukin (IL)-2, IL-13, and tumour necrosis factor-α, expression of major histocompatibility complex-2 (MHC-2) and caspase-1 in macrophages/monocytes, and increase MHC-1, CD40, CD80, CD89, and IL-12 in dendritic cells.[5] Although these mechanism(s) have the potential to produce antiviral actions, this will require rigorous experimental evaluation. In contrast, and as shown in a meta-analysis, proton pump inhibitors (PPIs) may aggravate COVID-19 as there was an association between current PPI use and incidence of SARS-CoV-2 infection and severity of COVID-19 when a Korean study was excluded.[6]

Intravenous anaesthetic agents and sedatives

Propofol

ACE2 may be upregulated when tissues are exposed to sedative concentrations ($\geq$10 μg ml^{-1}) for >6 h.[7] Propofol might inhibit SARS-CoV-2 entry as suggested for hydroxychloroquine.[8] In addition, clinically relevant concentrations of propofol may have Sig-1R antagonistic properties.[7] Moreover, propofol has both antioxidant and antiinflammatory actions and may reduce systemic inflammation and exert organ protection in COVID-19.[7]

Ketamine

Ketamine may interact with both Sig-1R and Sig-2R as an agonist. However, its affinities for Sig-1R (K_i=140 μM) and Sig-2R (K_i=26 μM) were in the supraclinical and clinical ranges, respectively.[9] As Sig-1R is the more important target in SARS-CoV-2 infection,[2] it is unlikely that ketamine exerts potent proviral actions. However, as ketamine has antiinflammatory actions, this agent may reduce the risk of SARS-CoV-2-induced cytokine storm.[10]

Haloperidol and droperidol

Clinically relevant concentrations of haloperidol, a butyrophenone, interacts with both Sig-1R and Sig-2R (K_i=0.33 nM and 26 nM, respectively)[11] as an antagonist to produce SARS-

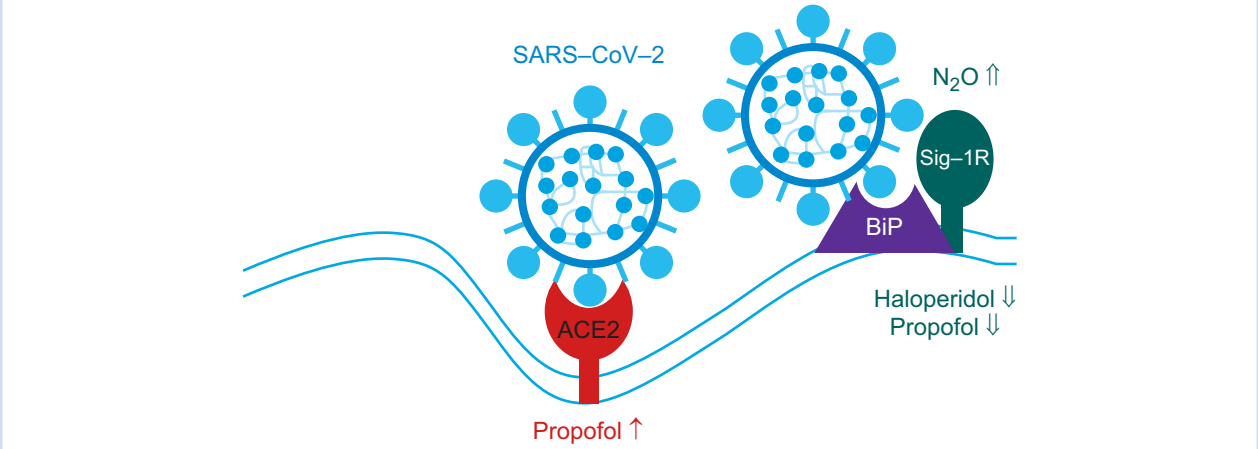

Fig 1. Cellular SARS-CoV-2 binding sites. ACE2, angiotensin converting enzyme 2; BiP, heavy chain binding immunoglobulin protein, also known as glucose regulating protein 78 (GRP78) or heat shock 70 kDa protein 5 (HSPA5) in the endoplasmic reticulum (ER); Sig-1R, sigma-1 receptor; ↑, upregulation; ⇑, activation; ⇓, inhibition.

CoV-2 antiviral actions.[2] Droperidol, another butyrophenone, interacts with Sig-1R as an antagonist but with a K_i of 0.17 μM, which exceeds clinically relevant concentrations.[12]

Dexmedetomidine

Dexmedetomidine displaced (+)[^{3}H]SKF-10047, a selective Sig-1R agonist, binding with a K_i of 5.7 μM[12] which exceeds clinically relevant concentrations.[13] Dexmedetomidine is therefore unlikely to affect SARS-CoV-2 infection via Sig-1R. However, the antiinflammatory and organ protective effects of dexmedetomidine[14] may provide therapeutic advantages for COVID-19 patients with multi-organ dysfunction in the ICU. The mechanism may hypothetically be attributable to inhibition of neutrophil extracellular traps formation (NETosis) to prevent immune activation in COVID-19.[14] Indeed, Stockton and Kyle-Sidell[15] reported a case of dexmedetomidine improving oxygenation and avoidance of tracheal intubation in a patient with progressive hypoxaemia.

Inhalation anaesthetic agents

Nitrous oxide, a Sig-R agonist,[16] might aggravate SARS-CoV-2 infection via Sig-R interaction. Regarding volatile anaesthetic agents, there are no reports detailing an interaction with ACE2 or Sig-R. A COVID-19 case series showed that isoflurane provided sufficient sedation and significant improvement in oxygenation without any adverse events.[17]

Local anaesthetic agents

COVID-19 patients often show high serum concentrations of citrullinated histone H3 (Cit-H3) which is a biomarker of NETosis. As serum from COVID-19 patients induces neutrophil extracellular traps (NETs) release from control neutrophils, COVID-19 may create a cellular environment for promotion of NETosis. I.V. lidocaine reduces blood neutrophil myeloperoxidase and Cit-H3[18]; this has the potential to attenuate an associated immunological storm.[19]

Opioids

Although chronic use or misuse of opioids leading to immunosuppression might increase the risk of SARS-CoV-2 infection,[20] opioids may attenuate respiratory symptoms in COVID-19 patients, such as shortness of breath and cough.[21] Moreover, opioids used in substitution therapy may aid in the maintenance of antioxidant capacity.[21] Opioids have the potential to exert both 'theoretical' beneficial and detrimental actions; further evaluation is required.

NSAIDs and paracetamol

WHO initially recommended that ibuprofen and other NSAIDs should be avoided in the management of COVID-19 symptoms, as there were anecdotal reports that NSAIDs such as ibuprofen could worsen the effects of SARS-CoV-2 during the early phase of COVID-19.[22] WHO later withdrew their recommendation because of a lack of clinical evidence.[22] Indeed, Rinott and colleagues[23] reported that ibuprofen use was not associated with worse clinical outcomes when compared with paracetamol or no antipyretic use.

Neuromuscular blocking drugs and their antagonists

Although neuromuscular blocking drugs and sugammadex are routinely used in the ICU and operating theatres, we are not aware of any reports showing proviral or antiviral actions of these agents in SARS-CoV-2.

Vasoactive drugs

It has been reported that β_2-adrenergic receptor activation produces antiinflammatory actions and suppresses immune function to impair bacterial clearance.[24] Vasoactive agents

with a β_2-adrenergic profile possess a theoretical risk for SARS-CoV-2 proliferation.

In conclusion, several *in vitro* experiments are suggestive that a number of anaesthetics and sedatives might affect SARS-CoV-2 infection via the ACE2 and Sig-R systems. Anaesthetists are concerned with potential risks of perioperative and ICU drugs; we have briefly covered potential risks in COVID-19 patients. Further studies to evaluate anaesthetic drug effects on (i) the ability of SARS-CoV-2 to infect and (ii) the ability of patients to mount an appropriate immune reaction are needed. Do anaesthetic agents exacerbate or ameliorate the effects of immune activation that have the potential to transition COVID-19 to long COVID?

Declarations of interest

DGL is Chairman of BJA. KH has no conflicts of interest to declare.

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