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Anaesthesia drugs, SARS-CoV-2, and the sigma-1 receptor: a complex affair. Comment on *Br J Anaesth* 2021; 127: e32–4

Amit Jain[1,*], Massimo Lamperti[1], D. John Doyle[2] and Francisco A. Lobo[1]

[1]Anesthesiology Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates and [2]Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA

*Corresponding author. E-mail: amitvasujain@gmail.com

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Editor—We enjoyed the article by Hirota and Lambert[1] postulating therapeutic potential for various anaesthesia drugs in COVID-19. However, we believe that the authors' approach of categorising these drugs as pro- or antiviral against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) based on sigma-1 receptor (Sig-1R) agonistic or antagonistic properties, respectively, is a potential oversimplification.

Although recent publications support antiviral properties for ligands with moderate to high affinity for Sig-1R, it is undetermined which pharmacological activity of Sig-1R ligands is responsible for inhibiting SARS-CoV-2 replication.[2,3] Considering the analogy that both κ-opioid receptor agonists and antagonists inhibit cocaine-induced replication of human immunodeficiency virus,[4] it may be possible that any ligand (i.e. agonist, antagonist, or allosteric modulator) with high affinity for Sig-1R could offer antiviral activity by competing with the viral proteins, thus preventing the hijacking of Sig-1R by SARS-CoV-2 non-structural protein 6 (nsp6).

As part of innate immune defences, macro-autophagy targets viruses and viral components for lysosomal degradation preventing virus-induced necrosis or apoptosis of the infected cell (Fig. 1), and exposes pathogen-associated molecular patterns to facilitate recognition. However, recent studies suggest that several strategies used by the SARS-CoV-2 virus exploit autophagy to promote viral replication while inhibiting degradation of viral proteins.[5] One key example is the interaction of SARS-CoV-2 nsp6 protein with Sig-1R.[3] Although the nature of the nsp6 interaction (i.e. agonistic or antagonistic or allosteric modulator) with Sig-1R remains unknown, this interaction induces the formation of double membrane vesicles and or autophagosomes carrying SARS-CoV-2 replication complex, but inhibits autolysosome formation.[2,3] Thus, SARS-CoV-2 induces defective autophagy and compromises the ability of autophagosomes to deliver viral components to lysosomes for subsequent degradation.[5,6] Defective autophagy may also impair antigen presentation, inhibit innate and adaptive immune responses, and reduce recycling of antiviral immune mediators.[6]

Sig-1R is a chaperone protein that is a key regulator of autophagosome–lysosome fusion, a common critical step in various forms of macro-autophagy and mitophagy, and degradation of defective mitochondria.[7] Although Sig-1R ablation reduces the fusion of autophagosomes and lysosomes and impairs autophagosome clearance without affecting upstream pathways, Sig-1R agonists promote effective autophagy.[7 8] In amyotrophic lateral sclerosis, Sig-1R mutants did not affect the formation of autophagosomes but produced aberrant accumulation of autophagic cargo, including defective mitochondria.[8] Mutant Sig-1R colocalises with accumulated autophagosomes, suggesting a role for Sig-1R in the fusion of autophagosomes and lysosomes.[8] Nonetheless, Sig-1R agonists improve autophagosome clearance by inducing autolysosome formation and provide clinical benefits in neurological and psychiatric disorders associated with impaired or defective autophagy.[9]

As SARS-CoV-2 utilises the nsp6 protein to support its replication by hijacking the Sig-1R to prevent autophagosome–lysosome fusion while activating omegasome formation,[6] it is possible that the nsp6 protein acts by mediating Sig-1R antagonism. We believe that high-affinity Sig-1R agonist ligands cannot only compete with nsp6 proteins for Sig-1R, but unlike Sig-1R antagonist ligands, these drugs also promote viral clearance and improve cell survival by supporting autophagic flux.[3] Notably, Sig-1R agonists are generally anti-inflammatory, reduce oxidative and endoplasmic reticulum stress, improve mitochondrial biogenesis, and reduce cytokine response, whereas Sig-1R antagonists oppositely affect these processes.[3,9] Although it is possible that both Sig-1R agonists and Sig-1R antagonists possess antiviral effects,[3] considering the above arguments and the fact that the only drugs that have shown any evidence-based benefits in COVID-19 disease outcomes are immunomodulatory or anti-inflammatory in nature (e.g. dexamethasone and tocilizumab), and that none of the clinically tested antiviral drugs has shown any mortality benefit (News – RECOVERY Trial), Sig-1R agonists may be a better option for treatment of COVID-19[3] (Fig. 1). This approach is supported by a clinical trial showing reduced risk of progression to severe COVID-19 in adults treated with fluvoxamine, a high-affinity Sig-1R agonist.[10] In contrast, haloperidol, a potent Sig-1R antagonist, failed to provide clinical benefit in COVID-19 patients.[10] Furthermore, Sig-1R knockout models are associated with increased mortality in sepsis, whereas fluvoxamine improved survival in lipopolysaccharide-treated mice.[11] Fluoxetine, another potent Sig-1R agonist, has been shown to inhibit SARS-CoV-2 replication, albeit by alternate mechanisms.[11] Similarly, the biased activity of dextromethorphan and haloperidol towards SARS-CoV-2 nsp6 is attributable to the different binding properties of these

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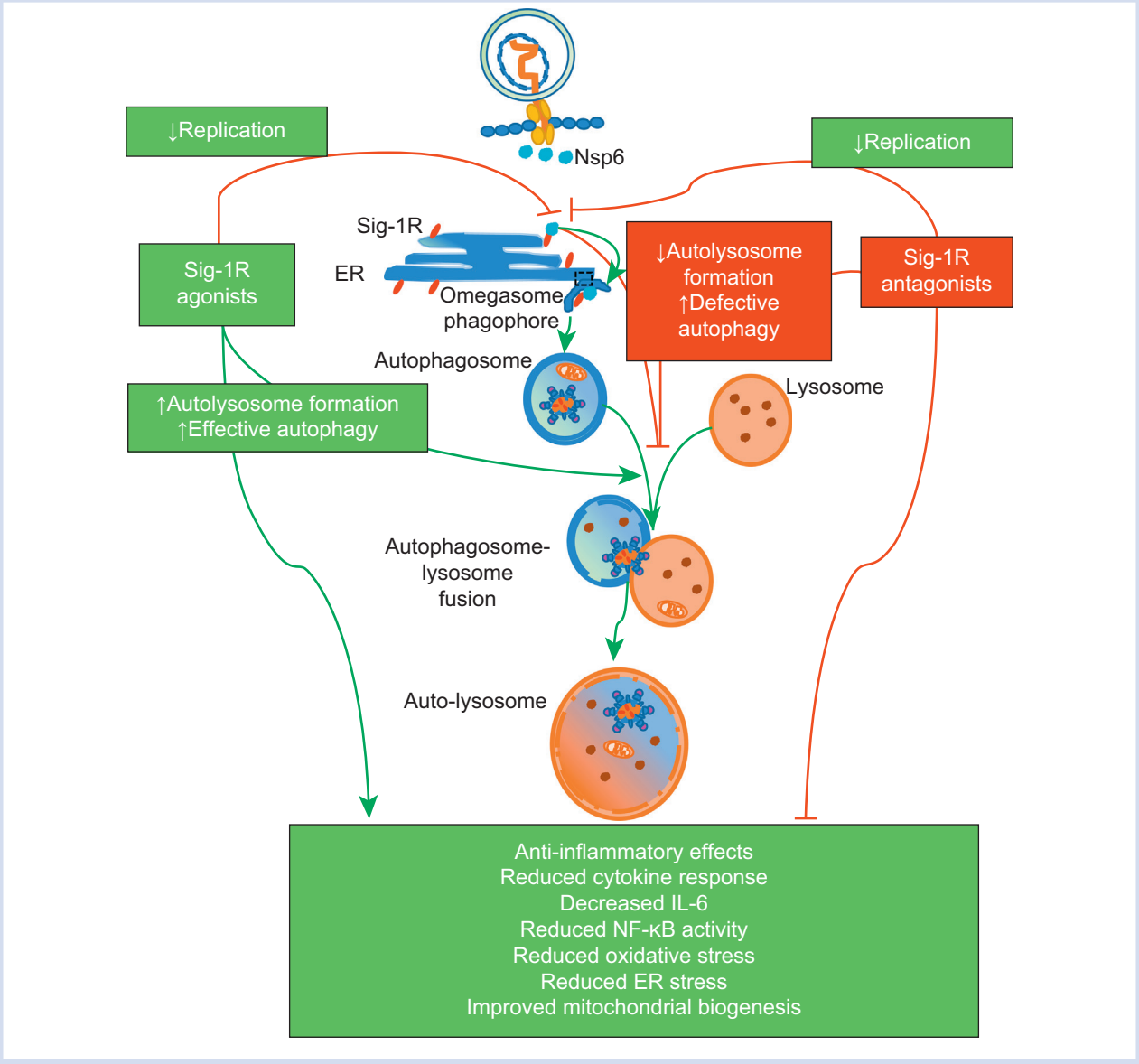

Fig 1. Diagram of the mechanisms of SARS-CoV-2 Nsp6 protein and Sig-1R interaction inducing defective autophagy, along with proposed mechanisms for Sig-1R agonists over Sig-1R antagonists for treating SARS-CoV-2 infections. Macro-autophagy is the main pathway, eradicating damaged organelles and viral particles. An early autophagy step is the formation of endoplasmic reticulum (ER) structures called omegasomes (highlighted as a dashed black box); these are the sites from which sack-like phagophores expand to accommodate substances destined for degradation by lysosomal-mediated macro-autophagy. SARS-CoV-2 Nsp6 proteins interact with Sig-1R to generate autophagosomes from the ER. The Nsp6–Sig-1R interaction also limits autophagosome expansion, compromising the ability of autophagosomes to deliver viral components to lysosomes for degradation. Immature double-membrane autophagosomes act as SARS-CoV-2 replication organelles. Sig-1R agonists may prevent Nsp6 protein binding with Sig-1R and induce autolysosome formation, promoting autophagy while inhibiting virus-induced defective autophagy. Sig-1R agonists also inhibit cytokine responses and promote cell survival. Sig-1R antagonists may prevent Nsp6-Sig-1R inhibition of virus-induced defective autophagy. However, cellular autophagy processes necessary to clear damaged organelles and misfolded proteins are also hampered, resulting in direct cytotoxic effects. ER, endoplasmic reticulum; IL-6, interlukin-6; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; nsp6, non-structural protein 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; Sig-1R, sigma-1 receptor. Red lines with blocked ends denote inhibition; green arrows denote activation.

drugs with the nsp6 protein[12] and is not secondary to their binding with Sig-1R. Hence, it may be possible that the antiviral effects of Sig-1R ligands are mediated by an alternate mechanism.[3] This makes it important to prefer anti-inflammatory Sig-1R agonists over pro-inflammatory Sig-1R antagonists in the treatment of COVID-19.[3] The argument is supported by the observation that Sig-1R antagonist NE-100 inhibited SARS-CoV-2 infection and replication in human

cardiomyocytes, but also disrupted cytoskeletal architecture and contractility.[13]

We thus believe that anaesthesia drugs with Sig-1R agonistic actions may be more beneficial against COVID-19 than those with Sig-1R antagonistic actions. As COVID-19 is a multisystem disorder with hyper-pro-inflammatory pathophysiology,[14] anaesthesia drugs such as dexmedetomidine that possess anti-inflammatory, cytoprotective, and organoprotective effects may be beneficial in COVID-19.[15] Apart from angiotensin converting enzyme 2 (ACE2) and Sig-1R, SARS-CoV-2 utilises other binding sites such as neuropilin-1 (NRP-1)[16] and sigma-2 receptor (Sig-2R)[17] for infecting host cells that may have limited association with anaesthesia drugs.

The SARS-CoV-2 spike protein CendR motif interacts with the b1b2 domain of NRP-1 to infect host cells including ACE2-deficient and TMPRSS2-negative endothelial cells.[16] This interaction can induce antinociception via subversion of the vascular endothelial growth factor (VEGF)/NRP-1 activity,[16] theoretically altering the potency of analgesics. Notably, hyperoxia can downregulate NRP-1, whereas dexmedetomidine reverses hyperoxia-induced NRP-1 downregulation and improves neuronal plasticity.[18] Whether this reflects in an increased SARS-CoV-2 cellular entry or in reduced neurological manifestations of COVID-19 warrants investigation. In addition, κ-opioid receptor agonists downregulate NRP-1 expression and inhibit VEGF signalling[19]; it is not clear if this is beneficial in controlling SARS-CoV-2 infection or COVID-19-associated angiogenesis. Finally, based on Auto-Dock Vina data, codeine and methyl-morphine have high binding affinities for ACE2 receptors,[20] although the antiviral role of opioids remains to be determined.

In a recent pre-print, Sig-2R was identified as a binding protein for SARS-CoV-2 viral protein Orf9c, and this interaction was found to increase Sig-2R/ACE2 complex formation and promote SARS-CoV-2 cell entry.[17] In the same study, Sig-2R ablation inhibited SARS-CoV-2 viral uptake, and decreased inflammatory and thrombotic effects in the modulation of the complement cascade.

In conclusion, at present it is unclear whether a Sig-1R agonist or Sig-1R antagonist would be better for inhibiting SARS-CoV-2 replication. Experiments comparing these ligands in the same assay are warranted. Until then, classifying anti-inflammatory anaesthesia drugs such as dexmedetomidine[21] as 'pro-viral' based on their agonistic activity on Sig-1R is not supported by evidence.

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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