ACE2 receptor, TRL-4 and SARS CoV-2: Do long acting opioids and opioid antagonists have potential for therapy?

Keywords: **ACE2 receptor, TRL-4, SARS CoV-2, COVID-19, opioids, opioid antagonists, Naltrexone**

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Abstract

Despite the advent of a vaccine, broadening the arsenal of drugs effective in the treatment and prevention of COVID-19 disease remains critical in the global effort to control the SARS-CoV2 pandemic. Opioids and opioid antagonists may have a role in treating and in the prevention of this disease based on a number of observations: an unexpectedly low incidence of COVID-19 has been observed in patients treated for opioid dependency with long acting opioid drugs such as methadone; opioids bind to the ACE2 transmembrane protein, a molecule that is widely considered to be main host cell receptor for SARS CoV2 cell entry; opioids have systemic immunomodulatory effects which may influence the response to the virus; studies aimed at repurposing drugs for treatment of COVID-19 have identified that opioids have therapeutic potential and finally there are ongoing trials of some of these drugs. The interaction of long acting opioids or opioid antagonists with the ACE2 receptor and the possible effects on TLR4 function in SARS CoV2 infection should be given serious consideration when developing effective therapies.

An unexpectedly low incidence of COVID-19 disease in opioid dependant patients has been reported (Eagleton et al 2020; EMCCDA May 2020; Welle Strand et al 2020). In this context, citing the widespread systemic effects of opioids on the immune system and their ability to stabilise cell redox balance, we have suggested the possibility of a protective effect of the long acting opioids or opioid antagonists used for opioid substitution treatment (methadone or buprenorphine with naloxone) on the clinical manifestation of SARS-CoV-2 (Eagleton et al 2020). The potential of naltrexone, an opioid antagonist, to modulate both the opioid and immune systems in the regulation of various disease processes has previously been proposed, Brown et al (2009). These authors suggested that low-dose naltrexone presented a safe and promising approach to the prevention and/or treatment of many autoimmune diseases and cancer variants, as well as various viral (e.g., AIDS) and neurological diseases (Multiple Sclerosis) that are exacerbated by compromised immunity.

The transmembrane angiotensin–converting enzyme (ACE2) is considered to be the main receptor for SARS-CoV-2 virus entry into host cells (Bourgonje et al 2020; Li et al 2020). The affinity of the SARS CoV-2 envelope spike protein (S) for the ACE2 receptor has been identified by *in vitro* studies, the same pathogenic mechanism as that identified during the SARS-Co-V and MERS epidemics (Datta et al 2020). Although ACE2 is established as an important receptor in viral infectivity, the relationship between expression of this protein and manifestation of disease remains to be fully elucidated (Chen et al; Li et al 2020). Datta et al 2020 in their recent review of therapeutic and vaccine targets related to blocking interaction of ACE2 and viral S protein, concluded that a better understanding of the ACE2 interaction with the S protein is required to develop enhanced therapeutics against COVID-19. Virtual screenings of compound libraries to identify molecules that may disrupt the host cell-virus interaction have been performed with the aim of repurposing existing drugs. The host ACE2 receptor has been identified as a potential binding target of some of these compounds (Choudhary et al 2020) and opioid and opioid antagonists have been identified in some of these studies as having an affinity for ACE2 receptor: Thirty eight Chinese patent drugs commonly used in respiratory disease, were examined in docking studies against the ACE2 receptor and viral main protease. These authors proposed that both morphine and codeine should be considered for clinical trials for treatment of SARS CoV-2 (Yan et al 2020). Roshanravan et al. (2020) in their review of SARS CoV-2 and the role of the ACE2 receptor,

concluded that the treatment of SARS-CoV-2 with ACE-2 inhibitory compounds is warranted and also suggested that both morphine and codeine may have a role. It is also interesting to note that *in vitro* ACE2 protein binds and cleaves the endogenous opioid peptide dynorphin A 1-13 (Vickers et al 2002). It is possible that opioids may prevent SARS-CoV2 entry into host cells by blocking the ACE2 receptor?

Li F. et al, (2020) using *in vitro* studies which examined molecular signalling pathways in SARS Co-V2 infected host lung cells, identified genetic pathways that become activated during infection and used this data, in conjunction with gene ontology studies and drug connectivity mapping to identify and rank existing drugs which could be re-purposed. Interestingly, the opioid antagonists , naloxone and naltrexone were identified among 65 drugs that could potentially inhibit these genetic pathways associated with viral infection. Moreover, a recent publication (Choubey et al., 2020) showed that *in vitro,* naltrexone suppressed production of pro-inflammatory cytokines and in docking simulation studies, demonstrated disruption of the interaction between ACE2 and the receptor binding domain of SARS-CoV-2 virus spike protein. These authors proposed repurposing FDA approved naltrexone at low dosage to treat patients with COVID-19.

In addition to the interaction of the SARS-CoV-2 with the ACE2 transmembrane protein described above, a link between toll-like receptor 4 (TLR4) signalling in host cells and COVID-19-mediated inflammation has also been observed (Sohn et al 2020). Matsayama et al 2020 in their review of transcription activator proteins in COVID-19 suggested that TLR4 is implicated in the pro-inflammatory response in COVID-19 which results in destruction of the architecture of the lung and could be a therapeutic target. The pro-inflammatory effects of opioids in the central nervous system and the consequent effects on analgesia have been extensively studied by Hutchinson (2007, 2008, 2008, 2010). These authors suggest that the pro-inflammatory effects of opioids can oppose the analgesic effects of these drugs and that these pro-inflammatory effects are mediated by TLR4. They suggest that a broad range of clinically relevant opioids including morphine, methadone and buprenorphine can activate TLR4. They also suggest that opioid antagonists (naloxone and naltrexone) are also antagonistic to TLR4 and oppose these pro-inflammatory effects in a non stereoselective way. (Hutchinson 2008 EJN). However other studies reject the evidence of interaction between TLR4 and opioids suggesting that opioids are exclusively immune suppressive (Eisenstein 2019). It is however pertinent that some authors have proposed opioids or opioid

analogues as potential therapeutics in COVID-19 (Tahatman 2020). Copolla and Mondola (2020) noted that bioflavinoids, which have an established affinity for opioid receptors, were identified in molecular docking studies to also have an affinity for the active site of the SARS CoV-2 protease and suggested that bioflavinoids could have role in treatment/prevention of SARS-CoV-2 of infection in opioid dependence.

While vaccination for COVID 19 is a very significant strategy in combating this disease, the worldwide roll-out of these programs for COVID-19 will take some time. It continues to be important to develop additional therapeutic strategies to treat and manage COVID-19 infections. We suggest that the interaction of long acting opioids or opioid antagonists with the ACE2 receptor potentially mitigates the effects of SARS CoV-2. The effects of these drugs on TLR4, which tend to be pro-inflammatory, and potential consequent effects on COVID-19 remain to be elucidated. It is interesting to note that the US National Library of Medicine website lists ongoing or planned trials of opioids and antagonists (including naltrexone and tramadol) for treatment of COVID-19 (NCT04604704; NCT04604678; NCT04365985; NCT04454307). Due to its safe non-addictive nature and longer duration of action, the opioid antagonist naltrexone in particular should be given serious consideration when developing effective therapies for COVID-19 disease.

Conflict of interests

The authors declare that they have no conflict of interest

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