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EDITORIAL



## Opioids/cannabinoids as a potential therapeutic approach in COVID-19 patients

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### 1. Introduction



Opioids and cannabinoids are a group of endogenous and exogenous compounds that function through activation of their respective receptors (opioid receptors:  $\mu$ ,  $\delta$ , and  $\kappa$ , cannabinoid receptors: CB1 and CB2) [1,2]. Besides their analgesia and psychoactive functions, opioid/cannabinoids systems have received remarkable attention since they can modulate the immune response, which affects immune-associated disease progression [3,4]. Modulation of the immune response by opioids/cannabinoids may be achieved through induction of apoptosis, suppression of cell proliferation, inhibition of pro-inflammatory and inflammatory cytokines/chemokines production, increase in anti-inflammatory cytokines, and induction of regulatory T cells [5,6]. *In vitro* and *in vivo* studies as well as findings in humans indicate that these systems positively or negatively affect viral replication and virus-mediated pathology. Depending on the type of virus, opioid/cannabinoid systems have different favorable and unfavorable effects on the outcome of the viral infection [7,8]. In viral infections where the host inflammatory response is pathogenic (known as immunopathogenic), activation of opioid/cannabinoid receptors is beneficial for control of immunopathology [7–9].

There are several pieces of evidence about the specific involvement of opioids/cannabinoids systems in respiratory viral-associated immunopathology and in modulating inflammation [7,8]. The data from our studies, for the first time, provided evidence that opioids/cannabinoids systems play an important role in respiratory syncytial virus (RSV) disease severity, which is the most common inflammatory disease in early childhood [10–12]. Immunopathogenesis of the RSV is one of the important aspects, causing severe illness in some cases since the infiltration of immune cells into the lung tissue and obstruction of the airways can lead to shortness of breath, bronchiolitis, pneumonia, and even death [13]. Using human studies and experimental models, we showed that opioids/cannabinoids signaling has a potentially beneficial role in the outcome of RSV disease. In these studies, the opioids/cannabinoids receptors blockade is associated with enhanced immunopathology, such as immune cell influx and increased cytokines/chemokines production, along with RSV-induced lung pathology and weight loss. However, activation of

these receptors using agonists decreased immune cell influx and cytokine/chemokine production, and alleviated lung pathology. Results suggest that the opioid system impairs or modulates immune responses induced by the influenza virus that might be beneficial for controlling viral immunopathogenesis [14,15]. Several studies also indicated that the lack of cannabinoid receptors could increase inflammation and tissue damage following influenza virus infection and their activation can impair immune responses induced by the virus [16–18]. Such data and effects of opioids/cannabinoids systems on other viruses such as HIV, HCV, HSV, and others [7,8] indicated that these systems may serve as therapeutic targets through the alleviation of virus-induced inflammation. How could we translate these data into the new coronavirus?

### 2. Opioids/cannabinoids systems and COVID-19

COVID-19 is a viral respiratory disease caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [19]. The emergence of SARS-CoV-2 in China at the end of 2019 has caused a large global outbreak that is a major public health problem with international concern [20]. At the moment, there is little data regarding the pathogenesis of SARS-CoV-2 and we only have informed guesses regarding the virus behavior. However, data from previous coronaviruses such as SARS-CoV and MERS-CoV indicated that a dysregulated/exuberant innate immune response is a leading contributor to the virus-mediated pathology [21]. Although a strong innate immune response is essential to eliminate viral pathogens, a prolonged or dysregulated/exuberant manner can damage the respiratory tract. It seems that besides underlying diseases, older age, and high viral titer, intensive inflammation correlates with adverse outcomes of SARS-CoV-2 infection [22]. In this regard, sustained inflammation (known as cytokine storm) has been observed in the majority of severe COVID-19 cases [23]. High concentrations of cytokines such as IL-2, IL-7, IL-10, G-SCF, IP10, MCP1, MIP1A, and TNF- $\alpha$  were recorded in plasma of

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critically ill patients infected with SARS-CoV-2, indicating that the cytokine storm could be associated with disease severity [24]. Importantly, while lymphopenia is a hallmark of COVID-19, there are numerous differences in laboratory findings between patients admitted to the intensive care unit (ICU) and those not admitted to the ICU, including higher white blood cell and neutrophil counts [25].

So far, no vaccine has been successfully developed and there is no effective treatment of COVID-19. Since intensive inflammation leads to disease-induced morbidity and mortality, inhibition of the hyperinflammatory response is a definitive drug therapy objective. Appealing evidence in similar infections and related diseases might pave the way toward rapidly COVID-19 growing pandemic. As an example, there have been reports regarding increasing interest in using IL-6 inhibitors (as a treatment for rheumatoid arthritis) to treat patients with severe COVID-19 infection, including a non-peer-reviewed retrospective Chinese experience describing 21 COVID-19 positive patients with severe illness who received tocilizumab. It is important to note that cytokine inhibitors are available and specific only for a few of the cytokines involved in the inflammatory cascade. Certainly, there is an urgent need for a substance that can potentially counter the effects of the virus and alleviate the symptoms and severity of the disease. Could opioids/cannabinoids be an effective treatment for COVID-19?

Infection is regulated by multiple cytokines that they act in concert to proceed with inflammatory responses. However, in some of viral infection, a storm of cytokines and chemokines occurs during infection that should take into account. It seems that in the case of severe COVID-19 patients balancing virus clearance and immunopathology through immunomodulators might be effective. Since opioids/cannabinoids receptors-based drugs can modulate immune cell migration and cytokine/chemokine secretion, they represent a promising pharmacological platform for developing anti-inflammatory therapeutics. Therefore in the absence of effective treatments to decrease the damage associated with COVID-19 especially in those admitted to the ICU and suffer from exaggerated inflammatory response, opioids/cannabinoids receptor agonists might potentially open up an effective therapeutic approach in COVID-19 infection. Notably, the biocompatibility, availability, and cheapness are considerable privileges of opioids/cannabinoids-based drugs. More research will be needed to determine which opioids/cannabinoids products and mixtures might be effective in treating COVID-19 and at what concentrations.

### 3. Expert opinion

It is interesting to remember that physicians in the late 19th century used anodynes of opium tincture as a treatment of 'bronchitis' and other ailments in infants and children, as case reports and experience 'demonstrated the efficacy' of the concoction in controlling coughing and facilitating breathing. Also, today some products of cannabinoids are used to modulate an inflammatory response. This permits us to rediscover the past and utilize the present, with hopes of finding the missing links in the pathophysiology of COVID-19, and raises the issue of opioids/cannabinoids utilization in the context of COVID-19. It is suggested that clinical trials could be

conducted on opioids/cannabinoids products with immunomodulatory activity. We hope that, with great efforts, scientific support, and sharing of information, the overcoming of COVID-19 will come soon.

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