EXPERT REVIEW OF RESPIRATORY MEDICINE
https://doi.org/10.1080/17476348.2020.1787836

Taylor & Francis
Taylor & Francis Group

EDITORIAL

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

Alireza Tahamtan[a,b], Masoumeh Tavakoli-Yaraki[c] and Vahid Salimi[d]

[a]Infectious Diseases Research Centre, Golestan University of Medical Sciences, Gorgan, Iran; [b]Department of Microbiology, School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran; [c]Department of Clinical Biochemistry, Cancer Research Laboratory, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran; [d]Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE HISTORY Received 3 May 2020; Accepted 18 June 2020

KEYWORDS Cannabinoids; COVID-19; immunomodulators; opioids; RSV

1. Introduction

Opioids and cannabinoids are a group of endogenous and exogenous compounds that function through activation of their respective receptors (opioid receptors: μ, δ, and κ, 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-α were recorded in plasma of critically ill patients infected with SARS-CoV-2, indicating that

CONTACT Alireza Tahamtan dr.tahamtan@goums.ac.ir Infectious Diseases Research Centre, Golestan University of Medical Sciences, Gorgan, Iran; Vahid Salimi vsalimi@tums.ac.ir Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

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.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Stein C. Opioid receptors. Annu Rev Med. 2016;67(1):433–451.
2. Lu H-C MK. An introduction to the endogenous cannabinoid system. Biol Psychiatry. 2016;79(7):516–525.
•• **This review is an introduction to the endocannabinoid system (ECS) with an emphasis on its role in synaptic plasticity**
3. McCarthy L, Wetzel M, Sliker JK, et al. Opioids, opioid receptors, and the immune response. Drug Alcohol Depend. 2001;62(2):111–123.
• **This is a good review article describing mu-, kappa-, and delta-opioid compounds are able to alter resistance to a variety of infectious agents.**
4. Tanasescu R, Constantinescu CS. Cannabinoids and the immune system: an overview. Immunobiology. 2010;215(8):588–597.
5. Rom S, Persidsky Y. Cannabinoid receptor 2: potential role in immunomodulation and neuroinflammation. J Neuroimmune Pharmacol. 2013;8(3):608–620.
6. Odunayo A, Dodam JR, Kerl ME, et al. State-of-the-art-review: immunomodulatory effects of opioids. J Vet Emerg Crit Car. 2010;20(4):376–385. .
7. Tahamtan A, Tavakoli-Yaraki M, Mokhtari-Azad T, et al. Opioids and viral infections: a double-edged sword. Front Microbiol. 2016;7:970.
8. Tahamtan A, Tavakoli-Yaraki M, Rygiel TP, et al. Effects of cannabinoids and their receptors on viral infections. J Med Virol. 2016;88(1):1–12.
9. Reiss CS. Cannabinoids and viral infections. Pharmaceuticals. 2010;3(6):1873–1886.
10. Salimi V, Hennus MP, Mokhtari-Azad T, et al. Opioid receptors control viral replication in the airways. Crit Care Med. 2013;41(1):205–214.
•• **This study show that opioid receptor signaling is required to control respiratory syncytial virus replication and thereby to control disease severity.**
11. Tahamtan A, Samieipoor Y, Nayeri FS, et al. Effects of cannabinoid receptor type 2 in respiratory syncytial virus infection in human subjects and mice. Virulence. 2018;9(1):217–230.
12. Tahamtan A, Tavakoli-Yaraki M, Shadab A, et al. The role of cannabinoid receptor 1 in the immunopathology of respiratory syncytial virus. Viral Immunol. 2018;31(4):292–298.
13. Openshaw PJM, Chiu C, Culley FJ, et al. Protective and harmful immunity to RSV infection. Annu Rev Immunol. 2017;35(1):501–532.
14. Coussons-Read ME, Daniels M, Gilmour MI. Morphine alters the immune response to influenza virus infection in Lewis rats. Drug Abuse Immun Aid. 1998;437:73–82.

- **This study demonstrate that morphine can alter immune function, and affect flu disease pathogenesis.**

15. Coussons-Read ME, Daniels M, Gilmour MI. Morphine reduces pulmonary inflammation in response to influenza infection. Life Sci. 1999;65(11):1141–1152.
16. Karmaus PW, Chen W, Crawford R, et al. Δ9-Tetrahydrocannabinol impairs the inflammatory response to influenza infection: role of antigen-presenting cells and the cannabinoid receptors 1 and 2. Toxicol Sci. 2013;131(2):419–433.
17. Buchweitz JP, Karmaus PW, Williams KJ, et al. Targeted deletion of cannabinoid receptors CB1 and CB2 produced enhanced inflammatory responses to influenza A/PR/8/34 in the absence and presence of Δ9-tetrahydrocannabinol. J Leukoc Biol. 2008;83 (3):785–796.
18. Karmaus PW, Chen W, Crawford RB, et al. Deletion of cannabinoid receptors 1 and 2 exacerbates APC function to increase inflammation and cellular immunity during influenza infection. J Leukoc Biol. 2011;90(5):983–995.
19. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–269.
20. Lai CC, Shih TP, Ko WC, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924.
21. Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. Immunol Res. 2014 Aug;59 (1–3):118–128.
- **In this review, the authors discuss the role of anti-virus CD4 and CD8 T cells during respiratory coronavirus infections with a special emphasis on emerging coronaviruses.**

22. Vaninov N. In the eye of the COVID-19 cytokine storm. Nat Publishing Group. 2020;20(5):277.
23. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes Infect. 2020 Mar;22(2):72–73.
24. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395 (10223):497–506.
25. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020 Feb 7;323 (11):1061–1069.
- **This study investigated the epidemiological and clinical characteristics of novel coronavirus (2019-nCoV)–infected pneumonia.**