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.

Medical Hypotheses 144 (2020) 110140

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

The possible immunoregulatory and anti-inflammatory effects of selective serotonin reuptake inhibitors in coronavirus disease patients

Mohammed Gaber Mohamed Hamed[a], Radwa Samir Hagag[b,*]

[a] Kafr Saad Central Hospital, Damietta, Faculty of Pharmacy, Tanta University, Egypt
[b] Pharmacy Practice Department, Faculty of Pharmacy, Egyptian Russian University, Cairo, Egypt

ARTICLE INFO

Keywords:
SSRIs
Depression
Pneumonia
Cytokines
COVID-19

ABSTRACT

While researchers are struggling to develop a vaccine for coronavirus disease, it is important to evolve effective therapeutic strategies to save lives. The majority of coronavirus disease deaths are due to pneumonia. Mostly, stress and depression are associated with coronavirus disease infection and thus, resulting in weakening of patients' immune response and hence, more severe respiratory symptoms or even death. We propose using a class of antidepressants named selective serotonin reuptake inhibitors for their reported potential antiviral effect, modulatory effect of respiratory symptoms, antioxidant properties and immunoregulatory effects beside their main action as antidepressant. In addition, the low cost of selective serotonin reuptake inhibitors might add a benefit for coronavirus disease patients.

Background about COVID-19

In December 2019, the world health organization (WHO) had reported a sudden elevation in the incidence of pneumonia in Wuhan city, China without a known relevant cause [1]. These raised levels in pneumonia cases were then attributed to the newly diagnosed coronavirus disease (COVID-19) which is caused by a highly contagious virus, that consequently resulted in a global pandemic infection in a relatively short duration [2]. COVID-19 can affect people both physically and mentally. WHO had announced that mental symptoms had aroused due to the public fear [3]. Studies had suggested that stress, anxiety and depression would be associated with COVID-19 infection [4,5].

The symptoms of COVID-19 had shown to range from mild or asymptomatic to severe. Most infected subjects had shown mild to moderate breathing problems and recover without vigorous treatment interventions. The severity of COVID-19 depends largely on the immunity and the release of inflammatory mediators [6].

Critically ill patients had shown symptoms of either mild or severe cytokine storms due to over activity of the immune system which is a major cause of death. This cytokine storm releases different inflammatory mediators, mainly IL-6 [13].

Early data regarding the current COVID-19 pandemic suggests that 60% of patients admitted to the intensive care unit (ICU) required mechanical ventilation, and the acute respiratory destress syndrome (ARDS) associated with pneumonia was diagnosed in about 40% of patients treated in the ICU [7]. Moreover, studies of COVID-19 had reported that pneumonia and ARDS are a consequence of coagulopathy and pulmonary embolus [8,9]. If ARDS could be prevented or mitigated, we can expect a significant reduction in COVID-19 associated mortality [10].

People of all ages may have an increased risk of serious illnesses and unfortunately, till now, there is no available vaccine to protect against COVID-19 and no definitive and effective radical treatment for COVID-19. Therefore, Ministry of health in the affected countries had advised their civils to protect their selves from exposure to the infected subjects [11,12].

Stress associated with COVID-19

The pandemic of COVID-19 has shown to affect people physically and psychologically [13]. The associated stress, anxiety and depression had shown to be responsible for a part in the pathogenesis of COVID-19 [14,15]. Stress is defined as the process by which environmental requirements transform the organism's adaptability, leading to psychological and biological changes [14]. Clinical evidences have proved an association between specific mood disorders, caused by sustained or chronic stress and the immune dysregulation [15–17].

A study conducted on COVID-19 patients had reported that the severe cases are caused by a malfunction or deficiency in the immune

* Corresponding author.
E-mail address: Radwahagag@yahoo.com (R.S. Hagag).

https://doi.org/10.1016/j.mehy.2020.110140
Received 15 July 2020; Received in revised form 19 July 2020; Accepted 23 July 2020
Available online 26 July 2020

system [18]. Immune dysregulation is a consequence of elevation of cortisol, the stress hormone, and reduction of serotonin [19]. This hormonal dysregulation might promote the initiation and progression of the infection [20].

In addition, stressful conditions associated with infection had shown to cause an elevation in the levels of the inflammatory mediator IL-6 that causes a decrease in the number and activity of cytotoxic T-cells and natural killer (NK) cells [21,22]. Moreover, the resulted depression due to prolonged stress was found to be associated with higher levels of serum IL-6 and tumor necrosis factor- alfa (TNF-α) [22], catecholamines, inhibitory T cells and histamine [14]. The decreased counts of lymphocytes, monocytes, eosinophils and basophils associated with depression had shown to participate more in suppressing the immune response [23,24].

These elevated inflammatory cytokines had shown also to precipitate depression and inflammations to many organs especially lung which is a serious condition and a main cause of mortality in COVID-19.

Serotonin role in regulating immunity and resistance to infection

Serotonin (5-HT) is a neurotransmitter and immunomodulator. It improves the mood and it is also responsible for feeling of happiness and calmness. 5-HT was found to regulate innate and adaptive immune responses. In addition, it has shown to play important roles in brain function, hemostasis, sleeping, mood regulation, behaviors and phycological state. It also has important roles in many different peripheral tissues, central nervous system (CNS) and immune cells [25,26]. The decrease in 5-HT levels is a major cause of depression like symptoms [27]

Pathological and physiological conditions may affect the role of serotonin in properly regulating the immune response [28]. Many researches had concluded that elevated serotonin levels plays a vital role in immunity against viral infections [29,30]. On the other hand, lowered levels of 5-HT had shown a correlation with susceptibility to bacterial infections [27].

COVID-19 had shown to increase the levels of pro-inflammatory cytokines [31]. These elevated levels had shown to increase the rate of metabolism of serotonin due to activation of indoleamine-2,3-dioxygenase (IDO) enzyme that metabolizes tryptophan which is the precursor of serotonin [32]. Moreover, studies had reported that the elevated levels of C-reactive protein (CRP) had shown to be linked to depression like symptoms [33–35].

Statement of hypothesis

Generally, antidepressants are found to augment the immune system response through inhibiting pro-inflammatory factors, in particular CRP, TNF-α, IL-1β and IL-6 [36]. Selective serotonin reuptake inhibitors (SSRIs) are used as antidepressants and anxiolytics by manipulating serotonin within the brain. SSRIs increase serotonin via proscribing its reuptake into the presynaptic cell then increasing the level of serotonin inside the synaptic cleft to bind the postsynaptic receptor [37].

SSRIs have shown an effective role in relieving symptoms of stress and anxiety, which enhances the role of immunity in confronting infection. This class had proved to prevent the elevation in cytokine levels which causes depression [38–41]. Moreover, SSRIs use had resulted in lowering endotoxin-induced fatigue [39]. *In vitro* antibacterial effect and modulation of antibiotic activity were also associated with using SSRIs [42–44].

In COVID-19 patients, SSRIs may help in hindering cytokine release syndrome that is responsible for aggravating sickness progression and the subsequent increase in TNFα [45]. A study had reported the effective role of SSRIs in severe chronic obstructive pulmonary disease where a significant increase of patients' oxygen saturation was observed [46].

Therefore, SSRIs family may help in controlling symptoms of COVID-19 patients due to its reported potent anti-inflammatory activity in different inflammatory disorders [39,47]

Antioxidant and anticoagulant properties of SSRIs

Many researches had reported the high therapeutic efficacy of SSRIs *via* reversal of the oxidative damage by the protective enhancement of antioxidant status following a stress-induced decline [48]. It has shown a significant inhibitory effect on nitric oxide (NO) production in a dose-dependent manner [49]. As a consequence, SSRIs had shown anti-inflammatory and analgesic properties [50].

SSRIs have shown anticoagulant properties [51] making it a promising option for COVID-19 patients who mostly experience venous and arterial thrombosis that is the major cause of mortality.

Antiviral properties of SSRIs

Given the high replicative potential of COVID-19, it is possible that the very high viral burden in the lung leads to a large inflammatory response which is fatal. Fortunately, SSRI was found to have antiviral effects beside being a mood stabilizer. A patent study had reported the efficiency of SSRIs treatment in reducing chemokine and cytokine expression in the infected cells and hence, it has a role in combating infections [52]. SSRIs had shown to potentiate the antiviral potency of certain antivirals [53]. SSRIs had reported HIV receptor and coreceptor downregulation [54], Ebola virus lowered activity [55] and reduced viral replication of Coxsackievirus B4 [56] by their use beside the antiviral.

Which SSRI are we going to use and why?

Sertraline is a member of SSRIs that is deeply suggested as a favorable therapeutic choice for COVID-19 patients because it has a wide therapeutic index and minimal anticholinergic activity which make it a safe option for elderly patients or those with underlying cardiovascular disorders [57].

Sertraline had strong anti-inflammatory effects via decreasing and regulating of pro-inflammatory cytokines [58,59]. It had significantly increased the activity of antibiotics with some resistant strains of *S. aureus, E. Coli* and *P. aeruginosa*. Thus, sertraline is a resistance modifying agent when used in combination with the antibiotics [44].

Also sertraline had reported antiviral efficacy [60] when used effectively in reducing influenza-induced lung inflammation and lowering mortality rate when combined with oseltamivir in a mouse model [53].

Regarding the ideal timing of starting sertraline, it would be advisable to start once respiratory symptom began to be worse or, in other words, before the onset of acute lung injury which precedes the occurrence of the fatal pneumonia.

Conclusions

In this hypothesis, we needed to raise the effective role of serotonin in the activation of T-cells and enhancement of the immune system in COVID-19 patients. This may show a high usefulness for the vulnerable subjects and medical staff who are constantly exposed to fatigue, stress, anxiety and depression caused by COVID-19 pandemic and had shown to destroy the immunity against any viral attack.

SSRI would play important roles in COVID-19 infection via treating anxiety and stress, and increasing the number and function of immune cells. Cytokine release syndrome in COVID-19 is expected to be ameliorated by the use of sertraline that lower IL-6 and IL-10 levels. Moreover, we suggest that sertraline may exhibit antiviral effect against COVID-19 but with unknown mechanism of action. We think that understanding the mechanism of halting the viral replication would be an

important research area that might benefit the scientific field.

We advise giving sertraline to moderate cases of COVID- 19 patients as a prophylaxis against lethal pulmonary symptoms and it should be used as an adjuvant therapy to drugs used in the protocol of COVID-19 treatment.

This research hypothesis would provide a great benefit in fastening the recovery and reducing mortality rates in COVID-19 patients. Moreover, if using sertraline is found to be effective in preventing the associated ARDS, its global use would be highly beneficial to the humanity. Besides, it is safe, tolerable and highly affordable.

Funding

This work is not granted or funded from any institution.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol 2020;92:401–2.
[2] Liu Y, Gayle AA, Wilder-Smith A, Rocklov J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med 2020;27.
[3] Coronavirus outbreak creating extra stress and anxiety for people with mental health problems, warns charity. https://www.independent.co.uk/life-style/health-and-families/coronavirus-stress-mental-health-problems-anxiety-covid-19-a9401061.html. [Last accessed on 11th July 2020].
[4] Cao W, Fang Z, Hou G, et al. The psychological impact of the COVID-19 epidemic on college students in China. J Psychiatr Res 2020;112934.
[5] Ozdin S, Bayrak OS. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemic in Turkish society: The importance of gender. Int J Soc Psychiatry 2020;20764020927051.
[6] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. China. Intensive Care Med 2020;46:846–8.
[7] Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708–20.
[8] Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J 2020;41. 1858-1858.
[9] Xie Y, Wang X, Yang P. COVID-19 complicated by acute pulmonary embolism. Radiol Cardiothorac Imaging 2020;2(2). e200067.
[10] McGonagle D, Sharif K, O'Regan A, Bridgewood C. Interleukin-6 use in COVID-19 pneumonia related macrophage activation syndrome. Autoimmun Rev 2020;102537.
[11] WHO. Coronavirus Overview. https://www.who.int/health-topics/coronavirus#tab=tab_1. [Last accessed on 11th July 2020].
[12] WHO. Coronavirus disease (COVID-19) advice for the public. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public. [Last accessed on 11th July 2020].
[13] Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res 2020;17:1729.
[14] Salleh MR. Life event, stress and illness. MJMS 2008;15:9.
[15] Jones KA, Thomsen C. The role of the innate immune system in psychiatric disorders. Mol Cell Neurosci 2013;53:52–62.
[16] Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Psychoneuroimmunology: Psychological influences on immune function and health. J Consult Clin Psychol 2002;70:537.
[17] Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. World J Biol Psychia 2003;54:269–82.
[18] Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. Cell Host Microbe 2020;27(992–1000):e1003.
[19] aan ht Rot M, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. CMAJ 2009;180:305–13.
[20] Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. J Neuroimmune Pharmacol 2006;1:421–7.
[21] Reiche EMV, Nunes SOV, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol 2004;5:617–25.
[22] Zorrilla EP, Luborsky L, McKay JR, et al. The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun 2001;15:199–226.
[23] Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020:ciaa248.
[24] Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020;7:11.
[25] Kubera M, Maes M, Kenis G, Kim YK, Lason W. Effects of serotonin and serotonergic agonists and antagonists on the production of tumor necrosis factor alpha and interleukin-6. Psychiatry Res 2005;134:251–8.
[26] Wan M, Ding L, Wang D, Han J, Gao P. Serotonin: A Potent Immune Cell Modulator in Autoimmune Diseases. Front Immunol 2020;11:186.
[27] Schuff-Werner P, Splettstoesser W. Antioxidative properties of serotonin and the bactericidal function of polymorphonuclear phagocytes. Tryptophan, Serotonin, and Melatonin. Springer; 1999. p. 321–5.
[28] Mössner R, Lesch K-PJB. behavior, and immunity. Role of serotonin in the immune system and in neuroimmune interactions. Brain Behav Immun 1998;12:249–71.
[29] Dursun S, Reveley MJMh. Serotonin hypothesis of psychiatric disorders during HIV infection. Am J Psychiatry 1995;44:263–7.
[30] Bliznakov E. Serotonin and its precursors as modulators of the immunological responsiveness in mice. J Med 1980;11:81.
[31] Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents 2020;34:1.
[32] Myint AM, Kim YK. Cytokine–serotonin interaction through IDO: a neurodegeneration hypothesis of depression. Med Hypotheses 2003;61:519–25.
[33] Frommberger UH, Bauer J, Haselbauer P, et al. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. Eur Arch Psychiatry Clin Neurosci 1997;247:228–33.
[34] Monje FJ, Cabatic M, Divisch I, et al. Constant darkness induces IL-6-dependent depression-like behavior through the NF-κB signaling pathway. J Neurosci 2011;31:9075–83.
[35] Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71:171–86.
[36] Eyre HA, Lavretsky H, Kartika J, Qassim A, Baune BT. Modulatory Effects of Antidepressant Classes on the Innate and Adaptive Immune System in Depression. Pharmacopsychiatry 2016;49:85–96.
[37] Leonard B. SSRI differentiation: pharmacology and pharmacokinetics. Hum Psychopharmacol 1995;10:S149–58.
[38] Wilson DR, Warise L. Cytokines and their role in depression. Biomed Rep. 2008;44:285–9.
[39] Hannestad J, DellaGioia N, Ortiz N, Pittman B, Bhagwagar ZJB. behavior, and immunity. Citalopram reduces endotoxin-induced fatigue. Brain Behav Immun 2011;25:256–9.
[40] Rizzo SS, Neal S, Hughes Z, et al. Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes. 2012;2:e199-e199.
[41] Wang L, Wang R, Liu L, Qiao D, Baldwin DS, Hou R. Effects of SSRIs on peripheral inflammatory markers in patients with major depressive disorder: A systematic review and meta-analysis. Brain Behav Immun 2019;79:24–38.
[42] Karine de Sousa A, Rocha JE, Goncalves de Souza T, Sampaio de Freitas T, Ribeiro-Filho J, Melo Coutinho HD. New roles of fluoxetine in pharmacology: Antibacterial effect and modulation of antibiotic activity. Microb Pathog 2018;123:368–71.
[43] Munoz-Bellido JL, Munoz-Criado S, Garcia-Rodriguez JA. Antimicrobial activity of psychotropic drugs: selective serotonin reuptake inhibitors. Int J Antimicrob Agents 2000;14:177–80.
[44] Ayaz M, Subhan F, Ahmed J, et al. Sertraline enhances the activity of antimicrobial agents against pathogens of clinical relevance. J Biol Res (Thessalon) 2015;22:4.
[45] Roumestan C, Michel A, Bichon F, et al. Anti-inflammatory properties of desipramine and fluoxetine. Respir Res 2007;8:35.
[46] Perna G, Cogo R, Bellodi L. Selective serotonin re-uptake inhibitors beyond psychiatry: Are they useful in the treatment of severe, chronic, obstructive pulmonary disease? Depress Anxiety 2004;20:203–4.
[47] Sacre S, Medghalchi M, Gregory B, Brennan F, Williams R. Fluoxetine and citalopram exhibit potent antiinflammatory activity in human and murine models of rheumatoid arthritis and inhibit toll-like receptors. Arthritis Rheum 2010;62:683–93.
[48] Zafir A, Banu N. Antioxidant potential of fluoxetine in comparison to Curcuma longa in restraint-stressed rats. 2007;572:23-31.
[49] Hashioka S, Klegeris A, Monji A, et al. Antidepressants inhibit interferon-gamma-induced microglial production of IL-6 and nitric oxide. Exp Neurol 2007;206:33–42.
[50] Abdel-Salam OM, Nofal SM, El-Shenawy SM. Evaluation of the anti-inflammatory and anti-nociceptive effects of different antidepressants in the rat. Pharmacol Res 2003;48:157–65.
[51] Halperin D, Reber G. Influence of antidepressants on hemostasis. Dialogues Clin Neurosci 2007;9:47–59.
[52] Sharma G, Altmeyer R, Pendharker V, Chen Y, Foley M, Compositions and methods for treating viral infections, Google Patents; 2010.
[53] Sharma G, Champalal Sharma D, Hwei Fen L, et al. Reduction of influenza virus-induced lung inflammation and mortality in animals treated with a phosophodiesterase-4 inhibitor and a selective serotonin reuptake inhibitor. Emerg Microbes Infect 2013;2:e54.
[54] Greeson JM, Gettes DR, Spitsin S, et al. The Selective Serotonin Reuptake Inhibitor Citalopram Decreases HIV Receptor and Coreceptor Expression in Immune Cells. Biol Psychiatry 2016;80:33.
[55] Johansen LM, DeWald LE, Shoemaker CJ, et al. A screen of approved drugs and molecular probes identifies therapeutics with anti–Ebola virus activity. Sci Transl Med 2015. 7:290ra289-290ra289.
[56] Alidjinou EK, Sané F, Bertin A, Caloone D, Hober D. Persistent infection of human pancreatic cells with Coxsackievirus B4 is cured by fluoxetine. Antiviral Res

2015;116:51–4.
[57] Murdoch D, Sertraline McTavish D. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depression and obsessive-compulsive disorder. Drugs 1992;44:604–24.
[58] Tynan RJ, Weidenhofer J, Hinwood M, Cairns MJ, Day TA, Walker FR. A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. Brain Behav Immun 2012;26:469–79.
[59] Lu Y, Xu X, Jiang T, et al. Sertraline ameliorates inflammation in CUMS mice and inhibits TNF-alpha-induced inflammation in microglia cells. Int Immunopharmacol 2019;67:119–28.
[60] Kouznetsova J, Sun W, Martinez-Romero C, et al. Identification of 53 compounds that block Ebola virus-like particle entry via a repurposing screen of approved drugs. Emerg Microbes Infect 2014;3:e84.