SSRIs: Applications in inflammatory lung disease and implications for COVID-19

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INTRODUCTION

The COVID-19 pandemic has led to press need for treatments and preventative strategies to manage acute and chronic lung disease. Given the rapid spread of COVID-19, it is expeditious to utilize medications that are already FDA-approved and that are known to have limited side effects. Selective serotonin reuptake inhibitors (SSRIs) have been explored as anti-inflammatory agents in the context of autoimmune and inflammatory diseases, and research suggests that SSRIs may inhibit inflammatory pathways implicated in acute and chronic lung disease. In this review, we will explore the utility of SSRIs in treatment and prevention of inflammatory lung disease and discuss the application of these findings to COVID-19.

PATHOGENESIS OF LUNG INFLAMMATION

COVID-19 is caused by the SARS-CoV-2 virus, an enveloped, single-stranded positive-sense RNA betacoronavirus. Alveolar macrophages detect viral components, leading to a T-cell-mediated immune response. Cells infected with the virus also stimulate interferon and cytokine release via interferon regulatory factor and transcription factor NF-κB activation, and recruit more immune cells to the site of infection. These immune cells propagate release of more proinflammatory molecules, leading to pulmonary and systemic disease.

COVID-19 presents a variety of problems to clinicians, including rapid onset of severe disease, various manifestations of pathology, and chronic obstructive pulmonary disease (COPD), describe the anti-inflammatory properties of SSRIs, and discuss the applications of SSRIS in treating COVID-19-associated inflammatory lung disease.

KEYWORDS

ARDS, COVID-19, lung inflammation, NF-κB, selective serotonin reuptake inhibitor

Abstract

Selective serotonin reuptake inhibitors (SSRIs) have anti-inflammatory properties that may have clinical utility in treating severe pulmonary manifestations of COVID-19. SSRIs exert anti-inflammatory effects at three mechanistic levels: (a) inhibition of proinflammatory transcription factor activity, including NF-κB and STAT3; (b) down-regulation of lung tissue damage and proinflammatory cell recruitment via inhibition of cytokines, including IL-6, IL-8, TNF-α, and IL-1β; and (c) direct suppression of inflammatory cells, including T cells, macrophages, and platelets. These pathways are implicated in the pathogenesis of COVID-19. In this review, we will compare the pathogenesis of lung inflammation in pulmonary diseases including COVID-19, ARDS, and chronic obstructive pulmonary disease (COPD), describe the anti-inflammatory properties of SSRIs, and discuss the applications of SSRIS in treating COVID-19-associated inflammatory lung disease.
and paucity of demonstrably effective treatments. SARS-CoV-2 infection initially manifests as fever, cough, and fatigue, among other symptoms, which can progress to severe pneumonia and hypoxic respiratory failure. On imaging, patients with COVID-19 have bilateral ground-glass opacities and upper lobe infiltrates associated with dyspnea and hypoxemia. These severe manifestations are mediated by several proinflammatory cytokines, including IL-6, TNF-α, IL-17, GM-CSF, and G-CSF. Cytokines involved in COVID-19 pathogenesis are summarized in Table 1.

Cytokine storm in COVID-19 infection can cause acute respiratory distress syndrome (ARDS), an inflammatory state in which increased vascular permeability leads to pulmonary edema and tissue destruction. A major cause of ARDS is sepsis secondary to bacterial pneumonia, influenza A and coronaviruses. ARDS is characterized by a primary insult, such as infection or trauma, leading to a secondary insult of inflammation and tissue damage. These insults cause capillary leakage in lung parenchyma which ultimately impairs oxygenation. Macrophages, endothelial cells, epithelial cells, and neutrophils release proinflammatory signaling molecules including IL-6, IL-8, TNF-α, and IL-1β, further increasing vascular permeability. More inflammatory cells are recruited, become activated and propagate the inflammatory response. Many cells and cytokines involved in the inflammatory response in ARDS pathology are implicated in COVID-19 infection and are summarized in Table 1.

Comorbid pulmonary disease, specifically chronic obstructive pulmonary disease (COPD), is an important risk factor for poor outcomes in COVID-19. Interestingly, patients with COVID-19 rarely reported comorbid COPD overall, potentially due to underdiagnosis. COPD and COVID-19 cause lung damage through a shared mechanism of increased inflammation, dysregulated immunity, and impaired repair function. These effects are summarized in Table 1 and Figure 1.

### 3.1 Selective serotonin reuptake inhibitors modulation of inflammatory transcription factors

Selective serotonin reuptake inhibitors alter the transcriptional regulation of genes encoding non-serotonergic neurotransmitter systems and inflammatory factors. Serotonin receptor activation decreases activity of signal transducer and activator of transcription 3 (STAT3) leading to reduced downstream expression of proinflammatory markers TNF-α, IL-1β, IL-6, and cyclooxygenase-2. The inhibitory effects of SSRIs on inflammatory transcription factors may have implications for treating inflammation-mediated damage caused by SARS-CoV-2 infection. In lung tissue, STAT3 and NF-κB are implicated in a variety of inflammatory processes including pathogen-induced acute lung injury, pulmonary inflammation, pulmonary fibrosis, and pulmonary vascular remodeling. SSRIs may decrease inflammation by suppressing the proinflammatory activities of STAT3, NF-κB, or both.

### 3.2 Selective serotonin reuptake inhibitors modulation of inflammatory cytokines

Patients with depression have been found to have increased levels of inflammatory cytokines at baseline and cytokines modulate the hypothalamic-pituitary-adrenocortical (HPA) axis leading to increased production of corticotropin releasing hormone and glucocorticoid receptor resistance. Loss of negative feedback at glucocorticoid receptors leads to dysregulated proinflammatory response. Fluoxetine inhibited HPA axis-mediated inflammatory edema in a rat model and clinical studies have demonstrated the ability of antidepressants to modulate glucocorticoid receptor function in humans.

Several specific proinflammatory cytokines are implicated in pathogenesis of depression. Levels of TNF-α, IL-6, and IFN-γ, among others, are significantly higher in patients with depression when compared to non-depressed controls. Among these, TNF-α, and IFN-γ reduce serotonin production and increase tryptophan and serotonin uptake in the brain, leading to overall depletion of serotonin and depression-like behavior. Conversely, serotonin influences macrophage activity in a dose-dependent manner, increasing production of IL-1 at physiologic concentrations of serotonin and inhibiting proinflammatory activity at elevated concentrations. Serotonin can, therefore, influence proinflammatory cytokine pathways, and SSRIs have been explored as immune modulators.

Selective serotonin reuptake inhibitors directly inhibit proinflammatory pathways. Administration of SSRIs inhibit TNF-α production in a mouse model of inflammation and impair TNF-α release from monocytes and microglia. TNF-α has neuromodulatory effects on norepinephrine secretion that are reversible with antidepressant administration. INF-α and IL-2 treatment induced reversible depressive symptoms in patients and administration of serotonin reduced TNF-α and IL-6 in human blood. SSRIs were able
| TABLE 1  Cytokines in the pathogenesis of lung disease and COVID-19 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | COVID-19         | ARDS            | COPD            | Pneumonia       |
| **Proinflammatory cytokines**  |                 |                 |                 |                 |
| IL-1β                           | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^176\) |
| IL-2                            | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| IL-6                            | Increased\(^3,7\) | Increased\(^3\) | Increased\(^14\) | Increased\(^17\) |
| IL-7                            | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| IL-8                            | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| IFN-γ                           | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| G-CSF                           | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| GM-CSF                          | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| TNF-α                           | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| **Chemokines**                  |                 |                 |                 |                 |
| IP10                            | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| MCP1                            | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| MIP1α                           | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| **Anti-inflammatory cytokines** |                 |                 |                 |                 |
| IL-4                            | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
| IL-10                           | Increased\(^7\) | Increased\(^7\) | Increased\(^17\) | Increased\(^178\) |
Selective serotonin reuptake inhibitors modulation of inflammatory cellular responses

Selective serotonin reuptake inhibitors inhibit presynaptic reuptake of serotonin to increase extracellular serotonin concentrations, thereby ameliorating depressive symptoms,\(^\text{112}\) and they also inhibit serotonin uptake by peripheral cells.\(^\text{110,112-115}\) Ninety five percent of the body’s serotonin is produced by enterochromaffin cells in the gut and plays a variety of secretory, sensorimotor, homeostatic, and immunologic roles.\(^\text{116,117}\) SSRIs block the serotonin transporter (SERT), expressed on platelets,\(^\text{118}\) T cells,\(^\text{119}\) macrophages,\(^\text{115}\) and other immune cells.\(^\text{117}\) SSRIs increase extracellular serotonin concentrations to exert indirect (serotonergic) activation of serotonin receptors.\(^\text{120}\) Platelets take up peripheral serotonin produced in enterochromaffin cells via SERT;\(^\text{121-123}\) and intracellular transport of serotonin molecules leads to platelet activation and aggregation.\(^\text{124,125}\) Release of platelet-derived serotonin modulates proinflammatory responses and activation of monocytes and T cells.\(^\text{126}\) Administration of SSRIs increased SERT expression on T cells in patients with depression, which inhibited T-cell proliferation and promoted apoptosis.\(^\text{119}\) SSRIs also directly suppress antigen-presenting cells.\(^\text{127}\) SSRIs also exert direct (non-serotonergic) activation of serotonin receptors through direct binding. Fluoxetine binds with high affinity to 5-HT\(_{2B}\) serotonin receptors to induce antidepressant effects that are abrogated in 5-HT\(_{2B}\) knockouts.\(^\text{128}\) Fluoxetine transitions macrophages from a proinflammatory M1 phenotype to an anti-inflammatory M2 phenotype.\(^\text{129}\)

4 | SELECTIVE SEROTONIN REUPTAKE INHIBITORS: IMPLICATIONS FOR COVID-19

Strategies to combat COVID-19 continue to develop, and treatments currently under investigation include antiviral and antimarial agents,\(^\text{12,130,131}\) immunosuppressant medications,\(^\text{6,132}\) and anti-IL-6 modulators.\(^\text{17,133,134}\) Olanzapine, an atypical antipsychotic and potent H1 antagonist, has been proposed as a therapeutic IL-6 modulator for COVID-19 infection.\(^\text{135}\) The inflammatory processes implicated in the pathogenesis of COVID-19 overlap with mechanisms in acute and chronic lung disease, and SSRIs modulate these pathways at several distinct points. Chronic administration of SSRIs reduce levels of IL-6 and TNF-\(\alpha\) to the degree that decreased IL-6 can be used as a marker for SRI efficacy.\(^\text{137}\) SSRIs, therefore, may have clinical utility in targeting IL-6 to treat COVID-19.

Selective serotonin reuptake inhibitors have been studied as modulators in lung disease. Fluoxetine was found to be protective.
against asthma and depression in a rat model,\textsuperscript{138} and patients with comorbid asthma and depression had improved asthma outcomes when treated with a SSRI.\textsuperscript{139} Fluoxetine also protects against chronic methamphetamine-induced pulmonary inflammation.\textsuperscript{140} Patients with COPD reported improvements in dyspnea when a SSRI was added,\textsuperscript{141-144} and improved walking distances correlated with improvements in depressive symptoms over time.\textsuperscript{145-147} SSRIs have therapeutic utility in pulmonary arterial hypertension (PAH), a common sequela of COPD associated with pulmonary vascular remodeling.\textsuperscript{148} Fluoxetine prevents and reverses PAH in mice\textsuperscript{149} and inhibits remodeling and inflammation in rat lung tissue.\textsuperscript{150} SSRI use correlated with 50% reduction in risk of death in patients with PAH,\textsuperscript{151} and baseline SSRI use was associated with a reduced incidence of PAH and decreased mortality in PAH.\textsuperscript{152} However, one study found increased morbidity and mortality among elderly adults who were newly started on a SSRI medication.\textsuperscript{153} A Cochrane review was unable to determine the efficacy and safety of SSRIs in COPD and recommends further study.\textsuperscript{142}

Patient appropriateness for the use of SSRIs is generally very broad, but caution should be used with certain comorbid illnesses and certainly patients should be aware of common side effects and less frequent serious risks. Significantly, patients on SSRIs for treatment of COVID-19 symptoms would likely require treatment for periods of days to weeks, rather than the treatment of months or years seen for their primary disease indications of depression and anxiety. SSRIS are among the most prescribed medications in the United States and have very benign safety profiles. Most side effects associated with SSRIs (including sexual dysfunction, drowsiness, weight gain, and insomnia) are mild and many resolve within a few weeks of initiating treatment.\textsuperscript{154} Other documented side effects include malaise and diminished mental energy,\textsuperscript{155} diarrhea, diaphoresis, syndrome of inappropriate antidiuretic hormone and hyponatremia,\textsuperscript{156} movement disorders,\textsuperscript{157,158} and cardiac QT prolongation\textsuperscript{159} although these are exceedingly rare. Chronic use of SSRIs has also been linked, but with very low incidence, to interstitial lung disease in elderly patients, especially women.\textsuperscript{160,161} SSRIs interact with antiplatelet medications including aspirin and clopidogrel\textsuperscript{162,163} and nonsteroidal anti-inflammatory drugs (NSAIDs)\textsuperscript{164,165} to prolong bleeding times in some patients.\textsuperscript{164,165} SSRIs have been linked to increased incidence of gastrointestinal and other bleeding incidents and should not be used in patients with an active life-threatening bleed.\textsuperscript{166} Many of the life-threatening complications of COVID-19 and ARDS are associated with blood clots and so these patients often receive antiplatelet and anticoagulant medications.\textsuperscript{167,168} SSRIS should not be coadministered with linezolid antibacterial treatment or other monoamine oxidase inhibitors due to the high risk for serotonin syndrome and caution should be used when combining SSRIs with other serotonergic medications including meperidine, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors.\textsuperscript{169}

Recent evidence strongly points to a role for acute brief use of SSRIs in COVID-19 positive patients to prevent serious complications such as hospitalization, intubation, and death. Ultimately, more clinical studies are needed to understand the potential risks and benefits associated with SSRI use in COVID-19.

5 | CONCLUSION

Selective serotonin reuptake inhibitors modulate inflammatory pathways that are shared in acute and chronic lung inflammation. SSRIs have therapeutic utility in pulmonary arterial hypertension (PAH), a common sequela of COPD associated with pulmonary vascular remodeling.\textsuperscript{148} Fluoxetine prevents and reverses PAH in mice\textsuperscript{149} and inhibits remodeling and inflammation in rat lung tissue.\textsuperscript{150} SSRI use correlated with 50% reduction in risk of death in patients with PAH,\textsuperscript{151} and baseline SSRI use was associated with a reduced incidence of PAH and decreased mortality in PAH.\textsuperscript{152} However, one study found increased morbidity and mortality among elderly adults who were newly started on an SSRI medication.\textsuperscript{153} A Cochrane review was unable to determine the efficacy and safety of SSRIs in COPD and recommends further study.\textsuperscript{142}

Clinicians must consider potential detrimental effects of medications. Most side effects associated with SSRIs (including sexual dysfunction, drowsiness, weight gain, and insomnia) are mild and resolve within a few weeks of initiating treatment.\textsuperscript{154} Other documented side effects include malaise and diminished mental energy,\textsuperscript{155} diarrhea, diaphoresis, syndrome of inappropriate antidiuretic hormone and hyponatremia,\textsuperscript{156} movement disorders,\textsuperscript{157,158} and cardiac QT prolongation\textsuperscript{159} although these are exceedingly rare. SSRIs have also been linked to interstitial lung disease in elderly patients, especially women.\textsuperscript{160,161} SSRIs interact with antiplatelet medications including aspirin and clopidogrel\textsuperscript{162,163} and nonsteroidal anti-inflammatory drugs (NSAIDs)\textsuperscript{164,165} and can cause serotonin syndrome when combined with other serotonergic medications including tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin-norepinephrine reuptake inhibitors.\textsuperscript{169} These are important considerations for patients presenting with COVID-19, especially as antiplatelet and anticoagulant medications are sometimes used in treatment of ARDS.\textsuperscript{167,168} Notably, however, high-quality randomized trials demonstrate SSRIs are not associated with increased bleeding events.\textsuperscript{170} Ultimately, clinical studies are needed to understand the potential risks and benefits associated with SSRI use in COVID-19.

CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

Claire Kyung Sun Meikle wrote and edited the manuscript. Justin Fortune Creeden wrote and edited the manuscript. Cheryl McCullumsmith wrote and edited the manuscript. Randall G. Worth edited the manuscript.
DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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