Immunological Interfaces: The COVID-19 Pandemic and Depression

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Since the start of the spread of the coronavirus disease 2019 (COVID-19) pandemic, an international effort has sought to better characterize associated extra-pulmonary health sequelae. The acute and or chronic detrimental impact of SARS-CoV-2 infection on mental health, especially depression, is increasingly described. Simultaneously the pandemic has influenced depressive symptomatology by modifying economic, social and political structures, in addition to affecting daily routines. In both cases, associated immunological perturbations favoring a pro-inflammatory state could underlie an increased risk for depressive symptomatology. A resultant elevation in global depressive burden could further tax mental health care infrastructure and contribute to a range of worse health outcomes including diminished quality of life. This suggests a critical and time-sensitive need to better understand immune interfaces between depression and COVID-19.

Keywords: depression, immunity, cytokine storm, cytokines, microglia, COVID-19, SARS- CoV-2, pandemic

INTRODUCTION

The unprecedented spread of SARS-CoV-2 has created a global emphasis on the immune system and its role in COVID-19 disease risk, outcomes and therapeutics (1). Yet the importance of immunity in human health has increasingly expanded beyond infectious diseases. Alterations in immunological activation are now recognized for their role in diverse disease states (2–4). Cytological patterns of innate and adaptive immunity can indicate severity of disease burden and risk for complications in infectious and non-infectious conditions (5, 6). In the field of mental health, various immune cell and cytokine subsets are implicated in the pathogenesis of schizophrenia, anxiety and depression (7, 8). Among these data, an immunologic milieu characterized by elevated systemic inflammation has been repeatedly associated with the development of depressive symptomatology (9).

Prior to SARS-CoV-2, depression was already a worldwide epidemic with considerable negative impact on morbidity and mortality. It is estimated that globally 350 million people are affected by depression, and it is a leading cause of disability (10, 11). In addition to lowered quality of life, depression may also contribute to a shortened lifespan (12). Over the last century, a variety of hypotheses have explored biological underpinnings of depression and potential opportunities for treatment and prevention. Alterations in immunological pathways, especially increased low-grade systemic inflammation, are now the subject of extensive academic research (13). In a subset of patients with depression, elevated systemic inflammation is proposed to play a substantial role in disease pathogenesis (14).

COVID-19 has the potential to induce widespread immunological effects as a direct result of infection and indirectly, independent of infection by modifying behavior and thought patterns. This may preferentially shift the immunological milieu toward an inflammatory state and predispose to higher rates of depressive symptomatology. The present review focuses on immune pathways linking COVID-19 infection with risk for depression as well as putative non-infectious immune mechanisms by which SARS-CoV-2 could increase depressive burden (**Figure 1**).

REVIEW OF RECENT LITERATURE

As the data around short and long-term consequences of the COVID-19 pandemic accumulate, evidence suggests an urgent need to focus on neuropsychiatric sequelae. Though over 1,800 publications jointly mention COVID-19 and depression, fewer than 100 discuss the terms "immunity," "depression" and "COVID-19." Themes in these articles include: the role of complementary therapies, the beneficial role of physical activity, and pharmacological consideration and bidirectional interactions between COVID-19 and depression with a focus on stress, cytokine storm, and long-term depressive outcomes related to SARS-CoV-2 infection.

The extant research includes mention of several complementary therapies purported to target shared immunological pathways in depression and COVID-19. These include the use of Ayurveda (15) traditional Chinese medicine (TCM) (16), and dietary interventions of curcumin (17) and omega-3 fatty acids (18). The use of selective serotonin reuptake inhibitors (SSRIs) (19) and oxytocin (20) in COVID-19 have also been considered for their immunomodulatory and mood-related properties, and the importance of exercise as an immunomodulator and potential anti-depressive has also been described (21).

Two recent reviews have focused specifically on molecular mechanisms linking immunity, COVID-19 and depression. In the first (22)) the authors emphasize parallel pathways of kynurenine (KYN) pathway activation by COVID-19 cytokine storm and angiotensin-converting enzyme 2 (ACE2) receptor effects in increased risk for depression. In the second (23), the authors emphasize the role of cytokine storm in potential psychological outcomes from COVID-19. Related molecular pathways are also briefly discussed in a recent cohort analysis (24).

EXISTING LINKS BETWEEN DEPRESSION AND SARS-COV-2

Worldwide, millions of cases of the infectious disease SARS-CoV-2 have been reported (25), accompanied by a near universal exposure to political, social and economic ripple effects. Early in the course of the pandemic, the immunological effects of the virus on human physiology were characterized by respiratory symptoms including severe pneumonia (26). In the coming months, extra-pulmonary manifestations of the virus

were better described. These included cardiovascular, metabolic, hematologic, neurologic and dermatologic pathologies (27). Additional research highlighted a tax on mental health as a potential consequence of acute infection (28).

Academic and public focus has also expanded to the long-term effect of SARS-CoV-2 infection on human health (29). This has been called "post-acute COVID-19" or "long COVID" (30). Those who experience persistent symptoms for weeks or months after acute infection number in the thousands, and have created Facebook self-help groups, adopting the terminology "Long-Haul COVID" to describe their ongoing battle with health issues including worse cognition, low exercise tolerance, sleep problems, autonomic dysfunction as well as worsened mental health and autoimmunities (31–33). A recent study (34) more explicitly linked depressive psychopathology 3 months after hospitalization for COVID-19 pneumonia with elevated baseline scores on an index of immune activation and inflammation.

Finally, attention has increasingly turned to the indirect ramifications of the virus. In globally disrupting routines, the economy, access to care and social dynamics, the pandemic could alter health outcomes for billions. Early data suggest these impacts may prove especially relevant for mental health. Health care workers managing COVID-19 patients in China reported increased psychological strain, including higher rates of depressive symptoms (35). A population-based analysis of depressive symptoms in the US found a 3-fold increase in symptoms during the COVID-19 pandemic compared to before (36). In a recent survey of 130 countries, the World Health Organization (37) reported widespread disruption of mental health service for vulnerable populations (25). Patients with preexisting mental health and physical health conditions may be at particular risk for pandemic-related depression, and low social support and socioeconomic position may also confer increased risk (38). Additionally depression may itself confer heightened risk for further immune-mediated depressive symptoms through increased vulnerability to inflammatory immune activation after psychosocial stress (39). A summary of recently published themes linking COVID-19, immunity and depression can be found in **Figure 2**.

IMMUNE DYSFUNCTION AND DEPRESSION

Early evidence that inflammation could precipitate depressive symptoms was derived from hepatitis patients receiving immunotherapy with interferon alpha. Many of these patients developed psychiatric symptoms including symptoms of depression (40). Subsequent research showed that administration of low-dose endotoxin (e.g., lipopolysaccharide (LPS)) increases systemic markers of inflammation including tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6) and symptoms of depression (41). Research additionally demonstrates correlation between elevated inflammatory cytokines and depressive symptoms (9), and increased levels of the inflammatory markers high-sensitivity C-reactive protein (hs-CRP) and IL-6 have been shown to be risk factors for subsequent depression (42, 43).
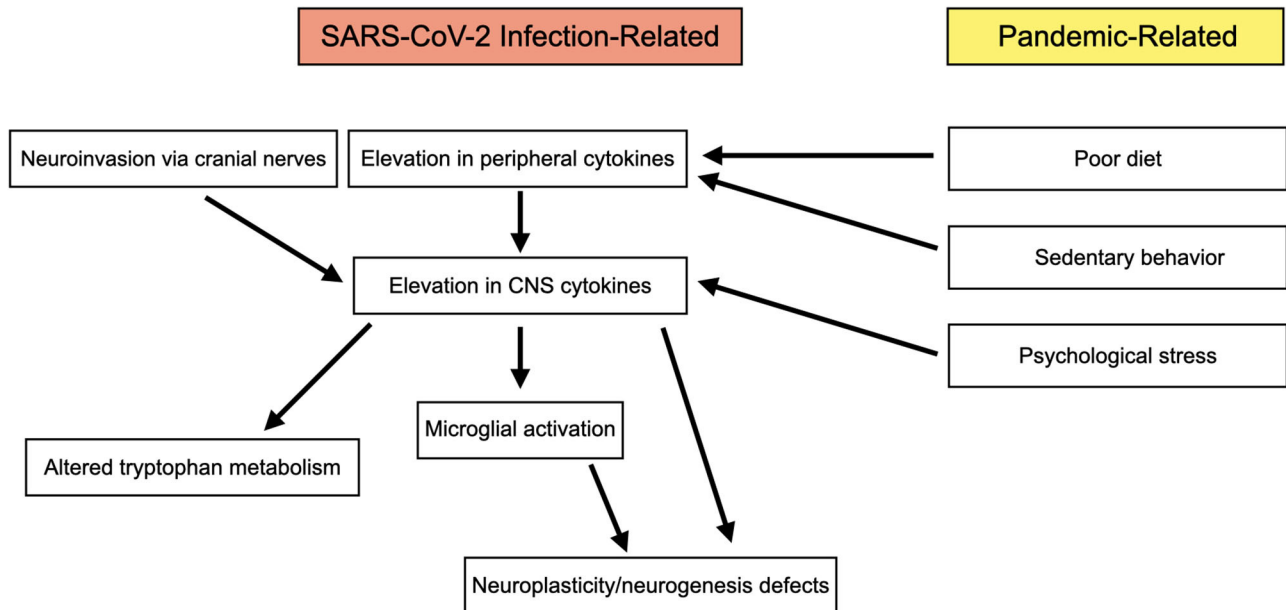
FIGURE 1 | Immunological pathways linking depression and COVID-19: Two convergent pathways connect the COVID-19 pandemic with altered immune function and depression. These include direct immunological implications of SARS-CoV-2 infection and indirect, non-infectious pandemic-related changes in immune function induced by poor diet, sedentary behavior and psychological stress. Both pathways may act to increase risk for depression by elevation of CNS cytokines and subsequently microglial activation, altered tryptophan metabolism and deficits in neuroplasticity and neurogenesis.

Brain alterations are central to the current understanding of depression pathophysiology (44). However, the brain is generally regarded as having immune privilege, which limits its exposure to peripheral immune states including inflammation (45). It is now understood that there are three methods by which peripheral inflammation may reach and influence the brain (46). These include cytokine passage through the blood brain barrier (BBB), cytokine activation of peripheral afferent nerve fibers returning to the central nervous system (CNS) and the trafficking of immune cells into the brain. In addition, CNS immune function can be directly activated when antigens enter thorough cranial nerves. For example, pathogens may reach the CNS by way of the olfactory and trigeminal nerves (45), and vagal afferent fibers convey immune-modulating signals from gut bacteria to the brain (46).

NEUROLOGICAL IMMUNE RESPONSE IN SARS-COV-2 INFECTION

In investigating the SARS-CoV-2 virus, research efforts have focused on the role of pre-existing immunological states as well as immune changes subsequent to infection. Direct correlations between COVID-19 outcomes and individual cytokines and immune cell populations indicate symptoms of COVID-19 are associated with elevations in interleukin 1 beta (IL-1β), IL-6, interleukin 10 (IL-10), and TNFα), as well as a general lymphopenia (47–49). Increased IL-6 may especially correlate with severity of COVID-19 (50).

An infection-related surge in proinflammatory mediators in COVID-19 has been called the cytokine storm or cytokine release syndrome. While consensus on the exact definition of the cytokine storm is debated, it is characterized by elevation in a range of immunological markers including interleukins, interferon-γ, TNF, chemokines and plasma proteins including complement and C-reactive protein (CRP) (51). In cytokine storm, hyperactivation of the inflammatory immune response may lead to significant collateral damage including respiratory distress, renal failure, liver injury and cardiomyopathy as well as neuropsychiatric issues (51). Up to 40% of people with COVID-19 have been reported to experience significant central nervous system (CNS) symptoms (52).

At this time, the precise methods by which the SARS-CoV-2 virus influences the CNS remain unclear. However, the widely cited symptoms of anosmia and dysgeusia suggest a high prevalence of CNS involvement (53), potentially via retrograde olfactory nerve transport (54). Research in prior coronaviruses has demonstrated coronavirus RNA in the human brain, suggesting a degree of neuroinvasion despite the virus's label as a respiratory pathogen (54). Peripheral immunological activation as a result of COVID-19 could also reach the CNS by transport through or disruption of the BBB (55, 56).
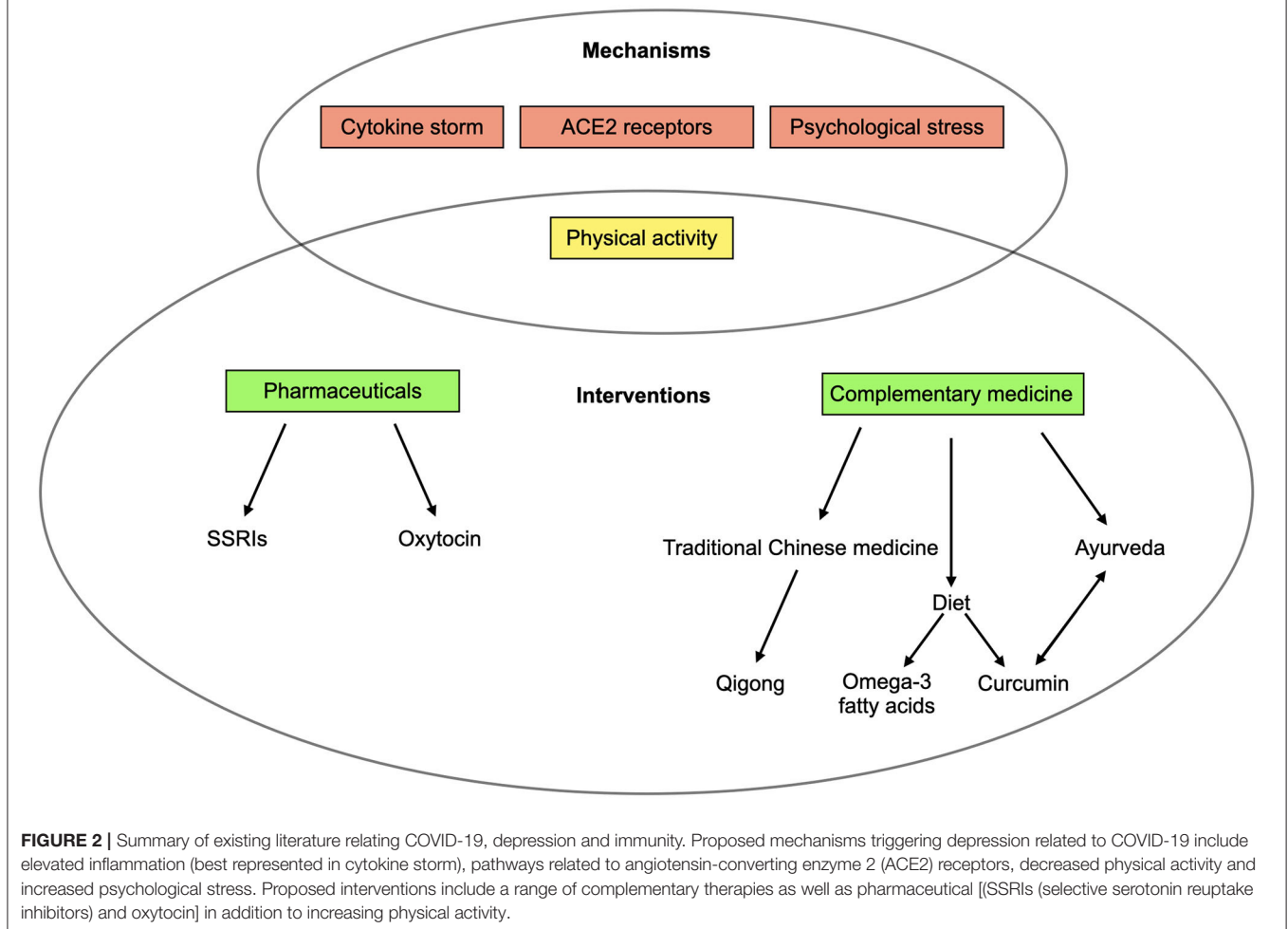
FIGURE 2 | Summary of existing literature relating COVID-19, depression and immunity. Proposed mechanisms triggering depression related to COVID-19 include elevated inflammation (best represented in cytokine storm), pathways related to angiotensin-converting enzyme 2 (ACE2) receptors, decreased physical activity and increased psychological stress. Proposed interventions include a range of complementary therapies as well as pharmaceutical [(SSRIs (selective serotonin reuptake inhibitors) and oxytocin] in addition to increasing physical activity.

On entering the CNS, peripherally generated inflammatory mediators may amplify their effects on the brain by acting on microglial cells. Microglial activation represents a transition from a state of relative quiescence to a "primed" state in which the microglia increase production of cytokines and other inflammatory mediators (57). Microglia are implicated in both acute and chronic neurological complications of COVID-19 infection (58), and increased microglial activation has been demonstrated in post-mortem neuropathological analysis of brain samples from COVID-19 patients (59, 60).

Those with existing neuroimmunological diseases may have heightened vulnerability to depressive symptomatology as a result of the COVID-19 pandemic. For example, people with multiple sclerosis demonstrated elevated rates of psychological distress including depression after easing of lockdown measures (61). Parkinson's disease has been strongly correlated with neuroimmune alterations including increased neuroinflammation (62), and a recent survey demonstrated high rates of depressive symptomatology in this demographic (63).

Additionally, patients with preexisting psychiatric diagnoses have been found to experience high rates of psychiatric symptoms including those related to depression in the context of COVID-19 lockdown measures, and immunological mechanisms have been proposed as a potential contributor (64).

Data demonstrating the long-term impact of COVID-19 on neuroimmune function remain limited. However, early survey results suggest that after acute infection, some experience residual symptoms of including fatigue, headache and anosmia, indicating a degree of persistent neurological alteration (65). Animal research implies a possibility for coronavirus-mediated neuronal damage as a result of alterations in glutamate homeostasis as well as potential for T cell-mediated demyeliation in susceptible hosts (66). SARS-CoV-2 infiltration of the olfactory bulb and subsequent polarization of microglial cells toward an inflammatory phenotype has also been proposed as a mechanism promoting neurodegenerative disease (67). As microglia mediate multiple neurological processes, chronic alterations in microglial populations as a result of COVID-19 could have significant

impact on multiple health outcomes including depression. While much investigative focus has been on direct links between viral infection and neuroimmune alterations in otherwise healthy individuals, those with existing neuroimmunological conditions may be especially vulnerable to non-infectious psychological stressors stemming from the pandemic.

NEUROPLASTICITY AND NEUROGENESIS

Neuroplasticity describes neural synaptic reorganization in response to environmental input. It is thought to form the basis for memory and learning (68). Impaired neuroplasticity is implicated in the pathogenesis of depression (69), a mechanism supported by alterations in brain functional connectivity (70) as well as loss of synapse-related genes and synapses in postmortem brain tissue of patients with depression (71).

Immune function is thought to exert a degree of control over neuroplasticity (72). This may occur in a dose-dependent manner with opposing effects at extremes of immune activation, as a low basal level of neuroinflammatory cytokines IL-1β and TNFα appears necessary for healthy neuroplasticity, with suppression at higher levels (73).

As regulators of CNS immunity, microglial cells are implicated in neuroplasticity. Microglia are thought to influence this process through glutamate homeostasis and production of inflammatory cytokines (74). On detection of homeostatic disturbance (e.g., metabolic, stress-related and pathogen-induced signals), microglia become activated, proliferating and producing inflammatory mediators (75). This may present a convergent mechanism by which peripheral immune activation and psychosocial stress could induce neuroinflammation, defects in neuroplasticity and eventually, depression.

Neurogenesis is the process of creating new neurons. Once thought restricted to early life, human research now shows that neurogenesis occurs in discrete zones of the brain into adulthood, including the hippocampus and lateral ventricle (76, 77). Like neuroplasticity, neurogenesis may underlie mechanisms of learning and memory (78). The neurogenesis hypothesis of depression proposes changes in the rate of neurogenesis in the subgranular zone of the dentate gyrus of the hippocampus in the pathophysiology of the disease (77).

Neuroplasticity and neurogenesis are affected by neurotrophic factors, compounds that bind to tyrosine kinase receptors and augment neuronal function, survival and development (79). Of these, much research has specifically focused on the role of brain-derived neurotrophic factor (BDNF) and its role in neuroplasticity, neurogenesis and depression (80, 81). Lowered levels of BDNF protein and BDNF gene expression are reported in both post-mortem brain tissue and in peripheral blood from depressed patients (82), and BDNF is increased by antidepressant therapies ranging from conventional antidepressants to electro-convulsive treatment (ECT) (83, 84).

Immunity plays a role in both BDNF expression and function. Administration of LPS reliably induces inflammation, including in the CNS (85). In animal models, LPS increases expression of inflammatory markers in the hippocampus and microglia

(86) and decreases levels of BDNF (87). It is also notable that microglial cells regulate release of BDNF (88).

The aforementioned pathway suggests a molecular mechanism by which infection with COVID-19 could directly downregulate levels of BDNF. However, non-infectious effects of the pandemic may also play a role, as chronic stress is thought to have a deleterious effect on BDNF expression (89). This implies that healthy neuroplasticity and neurogenesis may be compromised as a result of infection and psychological stressors generated by COVID-19 pandemic.

SEROTONIN AND TRYPTOPHAN METABOLISM

Decreased brain bioavailability of the tryptophan (TRP) metabolite serotonin (5-HT) underpins the psychopharmacology of the most commonly prescribed antidepressants (90). TRP metabolites including 5-HT engage in bidirectional interactions with the immune system.

5-HT may directly influence immune homeostasis by suppressing Th17 differentiation, increasing expression of T regulatory cells (Tregs) and promoting M2-polarization of macrophages (91). These immunological changes favor decreased inflammation and may speak to a role for serotonin in mediating inflammation-associated depressive symptoms.

More robust research focuses on the effects of immunity on TRP metabolism, including 5-HT availability. Enzymatic action on the essential amino acid TRP determines whether it is converted in 5-HT or shunted into the kynurenine (KYN) pathway. In general, the majority of tryptophan enters the KYN pathway, creating downstream metabolites including KYN, kynurenic acid (KYNA) and quinolinic acid (QUIN) (92).

Initiating enzymes in the KYN pathway are tryptophan 2,3-dioxygenase (TDO) and indolamine-2,3-dioxygenase (IDO). Notably, IDO is highly expressed in immune cells (93) and compared to TDO it is far more responsive to immunological signals (94). In the context of elevated pro-inflammatory cytokines including IL-1β and TNFα, IDO converts TRP to KYN, and shunts available TRP away from 5-HT production (95). Conversely, anti-inflammatory cytokines including interleukin 4 (IL-4) and IL-10 deactivate the IDO enzyme (96, 97). Recently, it has been proposed that by inducing cytokine storm and downregulating ACE2, the SARS-CoV-2 virus may increase levels of KYN pathways metabolites in the brain, increasing risk for depression (22).

The relative increase in KYN pathway activation as a result of inflammatory immune activation has been proposed to contribute to depression through 5-HT depletion, though more recent focus has shifted to the differential neuroactive effects of KYN metabolites (96). For example, KYNA may exert anti-depressant effects through N-Methyl-D-aspartate (NMDA) antagonist mechanisms resembling those of ketamine, while the NMDA agonist QUIN may have pro-depressive effects (96). While individual human trials are variable, there is some support for a decrease in KYNA and an increase in QUIN levels in depression (98).
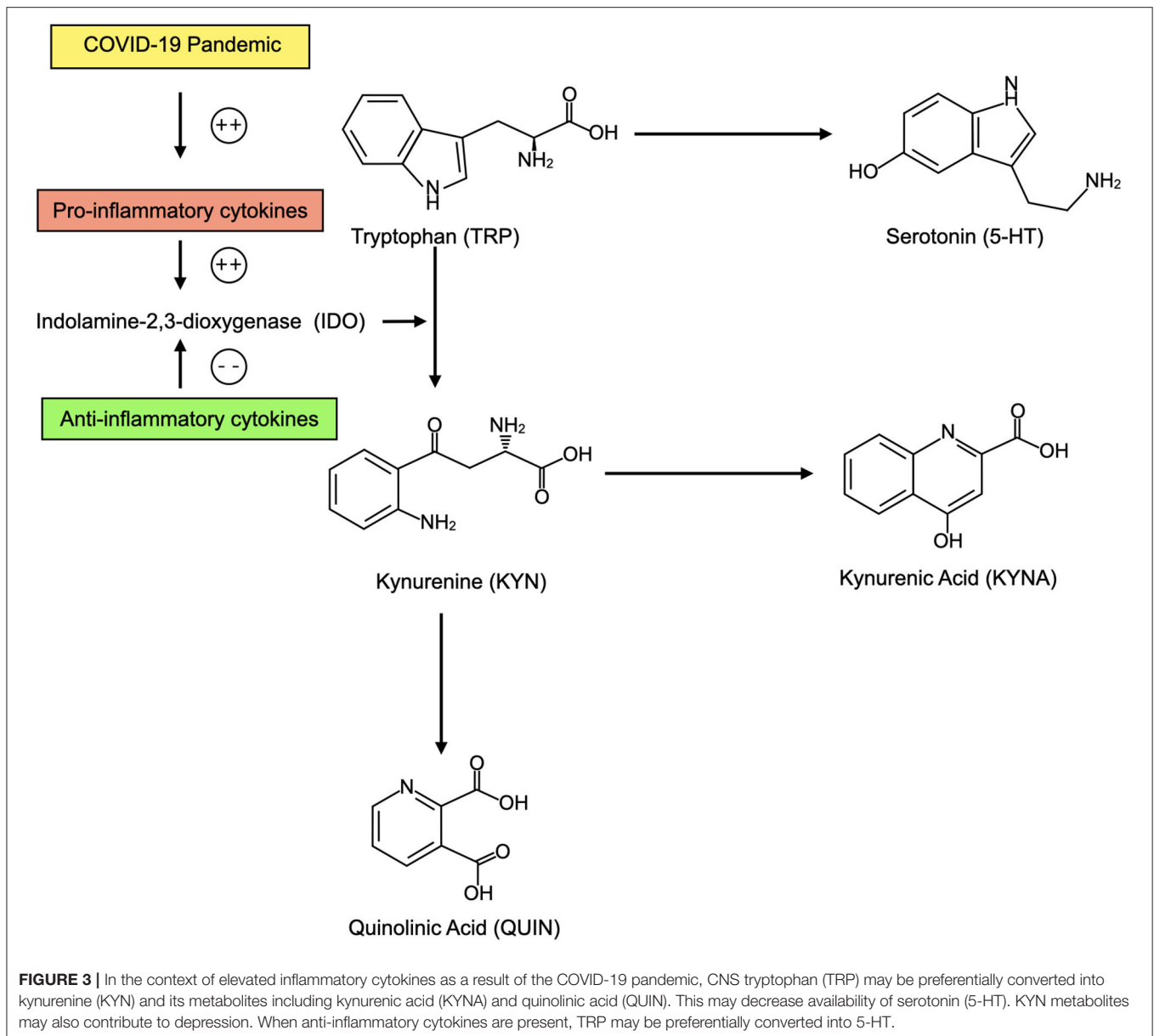
FIGURE 3 | In the context of elevated inflammatory cytokines as a result of the COVID-19 pandemic, CNS tryptophan (TRP) may be preferentially converted into kynurenine (KYN) and its metabolites including kynurenic acid (KYNA) and quinolinic acid (QUIN). This may decrease availability of serotonin (5-HT). KYN metabolites may also contribute to depression. When anti-inflammatory cytokines are present, TRP may be preferentially converted into 5-HT.

In sum, an elevation in systemic inflammation as the direct result of infection with SARS-CoV-2 or as a result of pandemic-related behavioral changes and psychological stressors could predispose to relative brain 5-HT depletion and imbalance in KYN pathway metabolites that increase risk for depression (**Figure 3**).

PSYCHOLOGICAL STRESS

Increased psychological stress has been widely documented in response to COVID-19. Personal diagnosis of or the diagnosis of a close contact with COVID-19 have each been associated with elevated stress as well as with increased symptoms of depression (99). Political measures taken to reduce the spread of the virus have been associated with elevated stress internationally (100, 101). Exposure to content related to COVID-19 has also been linked to increased psychological stress. In a survey of American

adults without prior history of a mental health condition, 15% reported 2 symptoms of psychological distress for at least 3 days in the past week, most commonly the sense of feeling nervous, anxious, or on edge (102). These symptoms were positively associated with social media and internet engagement with coronavirus content. Widespread food scarcity and economic instability as a result of the pandemic also pose a significant risk for elevated psychological stress (103).

Alterations in stress pathways including the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) are known risk factors for mental health conditions including anxiety and depression (104, 105). Early life exposure to major life stressors predicts a higher chance of developing depression in adulthood (106). At a cellular and molecular level, multiple stress-related alterations are seen in depression, including changes in levels of stress hormones, receptor expression of neurons and HPA responsiveness to

glucocorticoids (107–109). These changes may exert their effects on mood by way of immune modulation in the CNS (110).

Elevated psychological stress is proposed to induce immunological alterations through a variety of dose and duration-dependent mechanisms. Acute as well as chronic psychosocial stressors are associated with elevated inflammation (111). Acute stress correlates with elevation in plasma IL-6, TNFα, IL-1β and IL-10, while chronic stress has been linked to low-grade inflammatory activation including elevations in CRP, IL-6 and TNFα (111, 112). It is particularly topical that caregiving stress correlates with elevations in IL-6, while teacher burnout has been correlated with systemic inflammation along a continuum of symptom severity (Rohelder, 2019) (113).

Compared with acute stressors, chronic stress may better predict the low-grade inflammatory immune activation correlated with depression (114). Proposed linking mechanisms include glucocorticoid receptor resistance and subsequent inability to down-regulate inflammatory pathways as well as stress-induced production of inflammatory cytokines from visceral fat (115). Visceral fat expresses high levels of stress-related adrenergic receptors and produces pro-inflammatory cytokines including TNFα and IL-6 (116). Chronic stress may additionally cause microglia to adopt a pro-inflammatory phenotype, contributing to neuroinflammation (117). Inflammation may in part be mediated through stress activation of the NLRP3 inflammasome (118). Taken together, multiple mechanisms link COVID-19 pandemic-related psychological stress with an inflammatory immune state that could promote depressive symptomatology.

PHYSICAL ACTIVITY

COVID-19 related restrictions have sparked concern for decreased physical activity. In a recent survey of American adults, people active prior to COVID-19 restrictions reported a 32% reduction in physical activity (119). It is also notable that in this report, increased inactivity correlated with an increase in depressive symptoms. Similar results in American children suggest a decrease in physical activity and increase in sedentary activity since the spread of the pandemic within the United States (120).

Physical activity has been shown to be an effective therapy for unipolar depression, with a benefit comparable to antidepressants and psychotherapy (121, 122). Recently, existing data have been supplemented by Mendelian randomization techniques showing a potential causative role for the protective effect of physical activity in depression (123).

Physical activity is thought to positively affect multiple aspects of immune function, with a beneficial suppressive effect on inflammation (124). As exercise induces a transient elevation in inflammatory markers, these effects can appear paradoxical, and various explanations have been proposed. While acute exercise may rapidly increase inflammation, including levels of interleukin 1 (IL-1), TNFα and IL-6, these muscle-derived cytokines (myokines) may have local anti-inflammatory effect (125, 126). Though exercise increases IL-6 in the CNS, this is accompanied by a decrease in TNFα (127). It is suggested that IL-6 may therefore act as an anti-inflammatory cytokine in regions of the CNS by inhibiting TNFα, with an overall protective effect on neurons. Finally, exercise-induced elevation in inflammatory cytokines may be systemically balanced by a parallel increases in anti-inflammatory molecules, leading to a net anti-inflammatory effect (128).

DIET

Early research during the COVID-19 pandemic suggests the potential for a negative impact on dietary patterns, potentially as a response to increased chronic stress and changes in habits (129, 130). For example, an increased consumption of "comfort foods" has been reported in response to COVID-19 (131). A survey of Italians found that unhealthy dietary choices were driven in part by a desire to alleviate poor mental health (132).

In both children and adults, data indicate a COVID-19-related increase in intake of prototypically inflammatory foods including refined carbohydrates and sugary drinks and in adults, a decreased intake of fish and fruit (133–135). This change suggests that in response to the pandemic, there may a trend toward a Western pattern diet, which predicts higher levels of inflammatory markers including CRP and IL-6 (136) as well as increased risk for depression (137).

Dietary influences on immune function are diverse. The role of macro and micronutrient deficiency in immune dysfunction is well-characterized, and dietary fiber, omega-3 fatty acids and polyphenols are also purported to play a role in healthier immune function (138). Conversely, preclinical data suggest a deficit in dietary fiber could promote lower levels of Treg cells (139). Increased dietary saturated fat may facilitate inflammation by activation of the toll-like receptor (TLR4) signaling pathway, while omega-3 fats have the opposing effect (140). Additionally, immunity may be affected by changes in the gut microbiome (141) as well as more acutely by a lipid, glucose or dietary LPS-mediated postprandial inflammatory response (142). In the context of the aforementioned, it is notable that interventional trials promoting dietary patterns rich in whole foods and low in refined carbohydrates, fast foods, sweetened drinks and processed meats have demonstrated efficacy in decreasing depressive symptoms as well as in lowering inflammatory burden (143–146).

As a whole, these data suggest that changes in dietary patterns may represent a behavioral variable in inflammatory modulation, and that psychological stress-mediated trends during COVID-19 could have a detrimental effect on mood by increasing preference for less healthful foods. Emphasis on the consumption of a less processed diet and increased access to more nutrient-rich foods could represent a potential offset to diet-related immunological effects on depressive symptoms as a result of the pandemic.

DISCUSSION

Depression and COVID-19 demonstrate shared patterns of immunological function, especially around a pro-inflammatory

state characterized by elevation in cytokines including IL-6, TNFα, and IL-1β. SARS-CoV-2 may increase immunological risk for depression through direct infection-related influences on the CNS, or through associated behavioral shifts in diet, physical activity and psychological stress which subsequently promote an inflammatory immune state. Insight into the immunological intersections between depression and SARS-CoV-2 may help in the creation of strategies to mitigate of depression risk during the COVID-19 pandemic.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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