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Invited Review

Covid-19 interface with drug misuse and substance use disorders

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ABSTRACT

The coronavirus disease 2019 (Covid-19) pandemic intensified the already catastrophic drug overdose and substance use disorder (SUD) epidemic, signaling a syndemic as social isolation, economic and mental health distress, and disrupted treatment services disproportionally impacted this vulnerable population. Along with these social and societal factors, biological factors triggered by intense stress intertwined with incumbent overactivity of the immune system and the resulting inflammatory outcomes may impact the functional status of the central nervous system (CNS). We review the literature concerning SARS-CoV2 infiltration and infection in the CNS and the prospects of synergy between stress, inflammation, and kynurenine pathway function during illness and recovery from Covid-19. Taken together, inflammation and neuroimmune signaling, a consequence of Covid-19 infection, may dysregulate critical pathways and underlie maladaptive changes in the CNS, to exacerbate the development of neuropsychiatric symptoms and in the vulnerability to develop SUD.

This article is part of the special Issue on 'Vulnerabilities to Substance Abuse'.

1. Covid-19 and substance use disorder (SUD) syndemic

1.1. Introduction

Coronavirus disease 2019 (**Covid-19**) emerged as a world-historical pandemic which will change our lives for generations, and the end of this global crisis is not in sight. Covid-19 is the third coronavirus in the last 20 years to transmit from an animal reservoir to humans (Salajegheh Tazerji et al., 2020). The causative virus has been designated severe acute respiratory syndrome (**SARS**) coronavirus 2 (**SARS-CoV2**), a single-strand RNA virus. SARS-CoV2 is genetically close, but a distinct version of the viruses which caused the outbreak of SARS in 2003 and Middle East respiratory syndrome (**MERS**) in 2012 (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). The epidemiology and clinical findings to date suggest that Covid-19 presents with a wide spectrum of disease characteristics. The virus devastates host cell function in the lung, resulting in respiratory damage as a primary cause of death in some cases, despite mechanical ventilation to achieve lung recovery (Hanidziar and Bittner, 2020). Although the host risk factors are not yet completely clear, chronic comorbidities (e.g., diabetes, cardiovascular and pulmonary diseases) are thought to be key contributors to severe Covid-19 disease (Alhazzani et al., 2020; Qin et al., 2020; Zhao et al., 2020), potentially due in part to the exuberant inflammatory response to infection ("cytokine storm") (Stebbing et al., 2020). Additionally, neurological indicators of Covid-19 disease (e.g., confusion, delirium, dysphoria) have surfaced, suggesting that the central nervous system (**CNS**) involvement may contribute to the sustained pathophysiology of Covid-19 (Baig et al., 2020; Wu et al., 2020).

The synergism between two or more health conditions within the context of both disease and societal factors has been used frequently to understand the morbidity and mortality associated with human immunodeficiency virus (**HIV**) transmission and substance use disorders (**SUDs**) (Cisneros and Ghorpade, 2012; Sil et al., 2021; Tyagi et al., 2016). The syndemic concept is now relevant to the overlapping crises associated with the Covid-19 pandemic and the epidemic of abused drug misuse, overdose, and the incidence of SUDs. The Center for Disease Control and Prevention (**CDC**) reports that more than 33 million people have contracted SARS-CoV2 and nearly 600,000 individuals in the U.S. have succumbed to Covid-19 ((NCHS), 2021; Statistics, 2021; System, 2021). In parallel, drug overdose deaths claimed a reported 91,862 people in the U.S. in the 12-month period ending in October of 2020; up by ~30% vs. the previous year (provisional data) (Ahmad et al., 2021;

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Abbreviations

ACE2	angiotensin converting enzyme 2
AMYG	amygdala
ATP	adenosine triphosphate
BBB	blood brain barrier
CDC	Center for Disease Control and Prevention
CNS	central nervous system
Covid-19	Coronavirus disease 2019
CPP	conditioned place preference
CRF	corticotropin-releasing factor
CRP	*C*-reactive protein
CTSL	cathepsin-L
CXCL	chemokine (*C*-X-C motif) ligand
DDC	dopa decarboxylase
GC	glucocorticoids
GFAP	glial fibrillary acidic protein
hBMVEC	human brain microvascular endothelial cells
HIP	hippocampus
HLA-DR	human leukocyte antigen-DR isotype
HPA	hypothalamic-pituitary adrenal axis
IDO	indoleamine 2,3-di-oxygenase
IFN	interferon
IL	interleukin
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MHC	major histocompatibility complex
MCP-1	monocyte chemoattractant protein-1
MEM	multi experiment matrix
MERS-CoV	Middle Eastern respiratory syndrome coronavirus
MRI	magnetic resonance imaging
NAc	nucleus accumbens
NF-κB	nuclear factor-kappa B
NRP-1	neuropilin-1
PFC	prefrontal cortex
SARS-CoV	severe acute respiratory syndrome coronavirus disease
SUD	substance use disorder
TLR4	toll-like receptor 4
TMPRSS	transmembrane protease serine
TNF-α	tumor necrosis factor alpha
TPCN2	two-pore channel subtype 2
U·S	United States
VTA	ventral tegmental area
WHO	World Health Organization

Kuehn, 2021; Prevention, 2021). Recent surveillance data in the Overdose Detection Mapping Application Program shows an 18% rise in overdose deaths since the initiation of stay-at-home orders which correlates with increased of use in all types of substances of abuse (Alter and Yeager, 2020a).

The interaction between Covid-19 and SUDs also includes biological factors triggered by intense stress, intertwined with incumbent overactivity of the immune system, and resulting inflammatory outcomes. For instance, infection-triggered alterations in host immunity may drive key aspects of the psychopathology observed in the current Covid-19 pandemic which pose a significant vulnerability for the development of drug misuse and SUDs in recovering Covid-19 patients (Mazza et al., 2020). Preclinical research demonstrates that brain inflammation and viral-mediated immune activation, like that triggered by SAR-CoV2, result in maladaptive alterations in brain function which could drive drug misuse (Amruta et al., 2021; Blednov et al., 2011; Breese et al., 2008; Cannella et al., 2019; Eisenberger et al., 2010). Like other viruses, SARS-CoV2 immunopathology and disease progression are a function of factors that drive virus pathogenesis and host vulnerability (Ezeomah et al., 2020; Mangalmurti and Hunter, 2020). For example, host proteins involved in the pathogenesis of SARS-CoV2 infections, in parallel to host immune signaling, impact the kynurenine pathway, a major regulator of serotonergic and glutamatergic systems involved in SUDs and neuropsychiatric disorders; in tandem, kynurenine functionality is tightly regulated by inflammatory events (Anastasio et al., 2020; Attademo and Bernardini, 2021; Klempin et al., 2018; Linker et al., 2019; Morales-Puerto et al., 2021; Singer et al., 2012). Given that patient cytokine patterns and interferon responses correlate to Covid-19 disease severity and neurological complications, dysregulation of serotonergic and glutaminergic signaling could generate a cascade of pathophysiology that contributes to the escalation of SUDs (Galani et al., 2021; Kohno et al., 2019; Lucerne and Kiraly, 2021; Nennig and Schank, 2017; Solomon, 2021). Thus, Covid-19 medical risks factors due to dysregulated peripheral and CNS immunity, may increase the vulnerability to engage in drug abuse behaviors.

This mini-review highlights the relationship between inflammation and the kynurenine pathway in the CNS and the potential for vulnerability to SUDs following recovery from Covid-19 (Schematic 1) and focuses on elucidating aspects of immune-related consequences associated with SUDs.

1.2. Drug abuse and SUDs during Covid-19

The drug overdose crisis has resulted in the death of nearly 500,000 individuals between 1999 and 2018, the majority related to the opioid class of drugs [e.g., prescription pain relievers, synthetic opioids (fentanyl derivatives), heroin] (Upp and Waljee, 2020). In addition to opioid overdoses, cocaine- and methamphetamine-related fatalities increased nearly 30%, by approximately 10 deaths daily, between 1999 and 2018 (Hedegaard et al., 2020). Alarmingly, the CDC reported that 30% of overdose deaths involved a combination of stimulants and opioids and 10% involved stimulants alone (O'Donnell et al., 2020). Unfortunately, an 18.6% increase in non-fatal overdoses and an 11.4% increase in fatal overdose deaths have been observed during the stay-at-home orders in 2020 (Alter and Yeager, 2020b; Niles et al., 2021). Drug urine tests performed four months before and after the initiation of pandemic stay-at-home orders indicated increased prevalence of methamphetamine and cocaine use during the Covid-19 pandemic (Wainwright et al., 2020). In fact, the CDC estimates that 13.3% of people began using or increased use of abused substances as of June 2020 (Czeisler et al., 2020) and a self-described 34% increase in binge drinking by U.S. adults was also observed during the social isolation conditions of the pandemic (Weerakoon et al., 2021). About 40% of individuals increased tobacco use during the pandemic at a time that 71% of individuals indicated a heightened motivation to quit smoking tobacco and/or electronic cigarettes to reduce harms from Covid-19 (Kowitt et al., 2020). These indicators signal the potential for further elevations in drug overdoses and rises in the prevalence of SUDs.

Substance use disorders are diagnosed in the U.S. with the *Diagnostic and Statistical Manual of Mental Disorders-5* which outlines major SUD indicators (e.g., risky drug use, social/interpersonal difficulties linked to use, withdrawal/tolerance, failed efforts to control use, etc.) on a scale from mild to severe (Hasin et al., 2013); this nosology also includes craving (a strong desire or urge to take a drug) which is often triggered by cues associated with drug use (e.g., paraphernalia) and elevated stress levels (Koob, 2020; Koob and Volkow, 2016; Volkow et al., 2019). The intoxication induced by a psychoactive drug, when perceived as pleasurable, motivates the user toward episodes of intake, punctuated with escalating misuse and abuse, craving and/or withdrawal effects. This cycle can devolve into a diagnosis of a SUD in susceptible individuals. Termination of drug use and efforts to sustain abstinence can

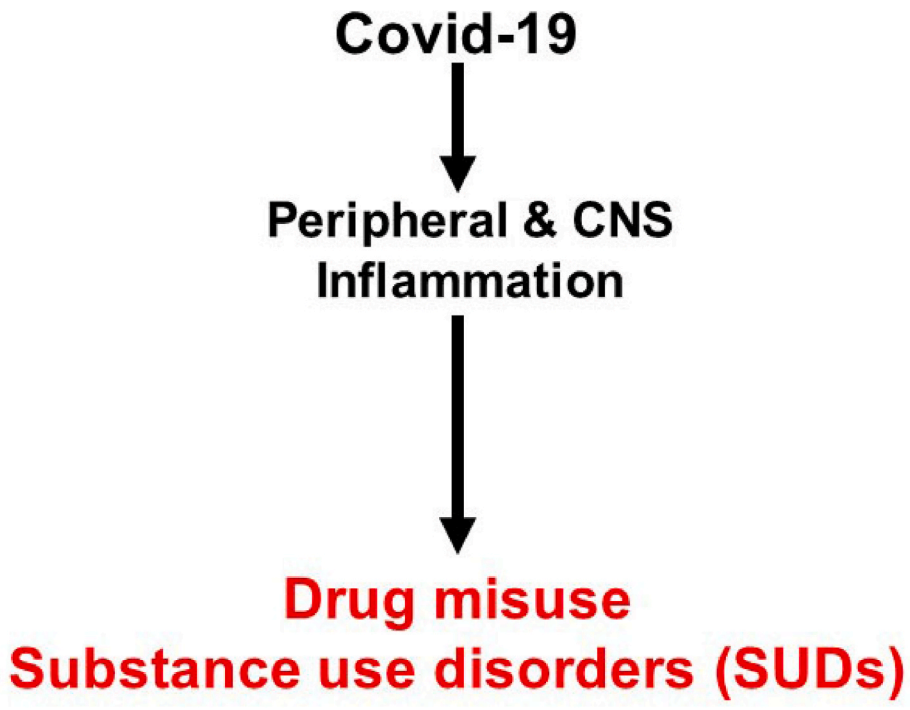
be marked by a high recidivism rate and reversion to drug-using behavior which interrupts the progress of abstinence and rehabilitation. The magnifying disorder that advances from drug use to misuse to SUD is linked to CNS pathophysiology which engages an "expanding cycle of dysfunction" in cognition, learning, reward, and emotion (Koob, 2020; Koob and Volkow, 2016; Volkow et al., 2019). Malfunctional synaptic plasticity in the CNS is a key pathological element in SUDs, which is dependent on the operational conversation across neurons, astrocytes, brain-resident microglia, and oligodendrocytes and is influenced by the neurovascular "unit" of endothelia and blood-born cells (leukocytes, platelets, erythrocytes) which carry peripheral immune cells and released pro- and anti-inflammatory cytokines and chemokines (Boulanger, 2009; He and Crews, 2008; Mahajan et al., 2008; Malaplate-Armand et al., 2005; Niu et al., 2019). The status of CNS immunological function is impacted by exposure to life stressors, like those associated with Covid-19 during stay-at-home orders and risk for contracting SARs-CoV2 infection, which evoke adaptations further impacting the experience of drug abuse (Clay and Parker, 2018; Koob and Kreek, 2007; Kreek et al., 2005; Vida et al., 2014; Wang et al., 2021b). The accumulation of these components likely contributes to an increased risk for drug misuse, overdose, and escalation of SUDs during the pandemic and following recovery from Covid-19. Disturbingly, 20% of respondents diagnosed with SUDs reported a consequent increase in drug use (Hulsey et al., 2020), elevating the challenges in sustaining abstinence and recovery and complicating efforts to reduce drug overdoses.

Increased drug use and misuse during the Covid-19 pandemic is likely attributable to a multitude of stressors including the intense anxiety about the dangers of becoming infected, the trauma of deaths and disabilities in communities, and the socioeconomic impact of lost employment (Taylor et al., 2021; Volkow and Blanco, 2021). In addition, the probability of a synergistic interaction between the immunological and inflammatory aspects of Covid-19 and the pathophysiology of SUDs cannot be discounted (Tien et al., 2011), especially given evidence to suggest that stress and drug misuse cycles promote the development of SUDs through elevated inflammatory cytokines (Blednov et al., 2015; Fox et al., 2012; Hueston et al., 2011; Loftis et al., 2013; Mandrekar et al., 2002; Truitt et al., 2016). Neurological consequences of Covid-19 may contribute to these rises in drug use and misuse and are potentially uncaptured side effects of Covid-19 illness that impedes full recovery. Thus, activation of CNS resident immune cells and amplification of inflammation, have a reciprocal effect on stress and substance abuse, which may be additive during co-morbidity and neurological sequalae of Covid-19.

2. Covid-19 neurological sequelae

2.1. SARS-CoV2 neurotropism

The Coronaviridae family of pathogen viruses present a clinical profile characterized primarily by respiratory involvement. However, SARs-CoV2 has the potential to be neuroinvasive based upon clinical, translational, and basic research conducted with SARS-CoV and the MERS-CoV (Arabi et al., 2015; Ng Kee Kwong et al., 2020). Multiple studies demonstrate that, aside from SARS-CoV2 acute respiratory engagement, SARS-CoV2 is neuroinvasive with observed CNS manifestations of Covid-19 (Bullen et al., 2020; Cantuti-Castelvetri et al., 2020; Jacob et al., 2020; Puelles et al., 2020; Ramani et al., 2020; Solomon et al., 2020; Song et al., 2021; Yang et al., 2020a). The mRNA for SARS-CoV2 was detected in human brain (Puelles et al., 2020; Solomon et al., 2020) and cortical neurons in autopsied patients who died of Covid-19 (Song et al., 2021). Viral SARS-CoV2 proteins were also found in endothelial cells of the olfactory bulb in human Covid-19 autopsies (Cantuti-Castelvetri et al., 2020). Several *in vitro* studies report SARS-CoV2 infection of human pluripotent stem cell-derived neural cells, human neurons of three-dimensional brain organoids, neural-perivascular assembloids, and neurospheres (Bullen et al., 2020; Jacob et al., 2020; Ramani et al., 2020; Song et al., 2021; Wang et al., 2021a; Yang et al., 2020a); however, the definitive routes of CNS infiltration for SARs-CoV2 remain to be identified. Thus, the virus invades neurons, and can be detected in CNS regions with direct connection to the point of entry in the olfactory mucosa, but other mechanisms and entry routes may allow *trans*-endothelial migration into brain parenchyma.



Schematic 1. Relationship between Covid-19, inflammation and SUDs. Inflammation and neuroimmune signaling related to Covid-19 infection underlay maladaptive changes within key brain regions involved in the formation of drug abuse and SUD behaviors.

Neuroinvasive dissemination routes of SARS-CoV2 are proposed to include olfactory transmucosal invasion by retrograde transport along sensory and olfactory nerves, thereby bypassing the blood brain barrier (**BBB**) (Baig et al., 2020). Alternatively, the hematogenous route *via* the systemic circulatory system may allow SARS-CoV2 to disseminate into the CNS *via* transcellular/paracellular migration or the Trojan horse strategy through host phagocytes (Perrin et al., 2021). Moreover, SARS-CoV2 interacts with key human host factors including angiotensin-converting enzyme 2 (**ACE2**) receptor, transmembrane protease serine (**TMPRSS**) 2/4, cathepsin L (**CTSL**), two-pore channel subtype 2 (**TPCN2**), and neuropilin-1 (**NRP-1**) to trigger target cell and organ invasion (Matschke et al., 2020). *In silico* analyses revealed the highest expression of ACE2 localizes to oligodendrocytes, NRP-1 and TPCN2 to astrocytes, CTSL to microglia, TMPRSS2/4 to neurons and NRP-1 to endothelial cells of the brain (Matschke et al., 2020). These host factors are implicated in viral tropism to the CNS. In brain tissue collected from postmortem Covid-19 patients, common neuropathological findings included astrogliosis in multiple brain regions, microglial activation, and infiltration of cytotoxic T-lymphocytes in the brainstem and cerebellum which point to clinical findings suggestive of viral and autoimmune encephalitis (Matschke et al., 2020). These authors also reported the detection of SARS-CoV2 RNA and viral proteins in the brains of 53% of the fatalities (Ludlow et al., 2016; Matschke et al., 2020). Therefore, detection of SARS-CoV2 RNA, protein, and CNS localized host proteins including ACE2, TMPRSS2/4, CTSL, TPCN2 and NRP-1, suggest that SARS-CoV2 can infiltrate the CNS, activating neuroimmune signaling through host proteins.

2.2. Host immunity and CNS immune signaling in Covid-19

Elevated levels of the circulating pro- and anti-inflammatory proteins (i.e. cytokines and chemokines), such as interleukin (**IL**)-1β, IL-4, IL-6, IL-10, interferon (**IFN**)-γ, tumor necrosis factor (**TNF**)-α, chemokine (***C*-X-C**) ligand (**CXCL**)10, and monocyte chemoattractant (**MCP**)-1 have been measured during the clinical course of Covid-19 (Bouadma et al., 2020; Bronte et al., 2020; Han et al., 2020; La Rosée et al., 2020). High concentrations of cytokines appear related to the more severe cases of Covid-19 based upon epidemiological evidence (Huang et al., 2020a; Ludlow et al., 2016). Despite the identification of SARS-CoV2 RNA and viral proteins in the brains of patients who died of Covid-19, little clinical data are available to firmly establish the nature and extent of inflammatory-specific events in the CNS. However, recent findings suggest SARS-CoV2-associated CNS inflammation given observations of a high degree of astrogliosis, microglial activation and localization of microglial nodules in the brainstem and cerebellum in postmortem Covid-19 patients (Matschke et al., 2020). Magnetic resonance imaging scans revealed reactive astrogliosis in postmortem brains (Coolen et al., 2020; Kanberg et al., 2020) and increased glial fibrillary acidic protein levels in plasma of patients who succumbed to Covid-19 (Coolen et al., 2020; Kanberg et al., 2020), indicating pathological events occurring in the CNS (Brommeland et al., 2007; Nylén et al., 2006; Quddusi and Shamim, 2019; Watanabe et al., 2019). Positive staining for Major Histocompatibility Complexes (**MHC**) or MHC class II cell surface receptor and the human leukocyte antigen-DR isotype (**HLA-DR**) in the CNS of patients who died from Covid-19 suggests activation of host immunity in the CNS (Aliseychik et al., 2018; Matschke et al., 2020). Lastly, release of multiple inflammatory cytokines and chemokines (IL-1β, IFN-α2, IFN-γ, TNF-α, MCP-1, IL-6, IL-10, IL-12p70, IL-17 A, IL-18, IL-23, IL-33) were generated by SARS-CoV2 exposure of human brain microvascular endothelial cells (**hBMVECs**), an *in vitro* model of the BBB (Reynolds and Mahajan, 2021). Considering previous evidence of activated CNS immune signaling associated with SARS and MERS infection, this cross-section of recent findings illustrates that SARs-CoV2 profoundly impacts immunological function in the brain.

3. SARS-CoV2 host factors and immune-kynurenine pathways

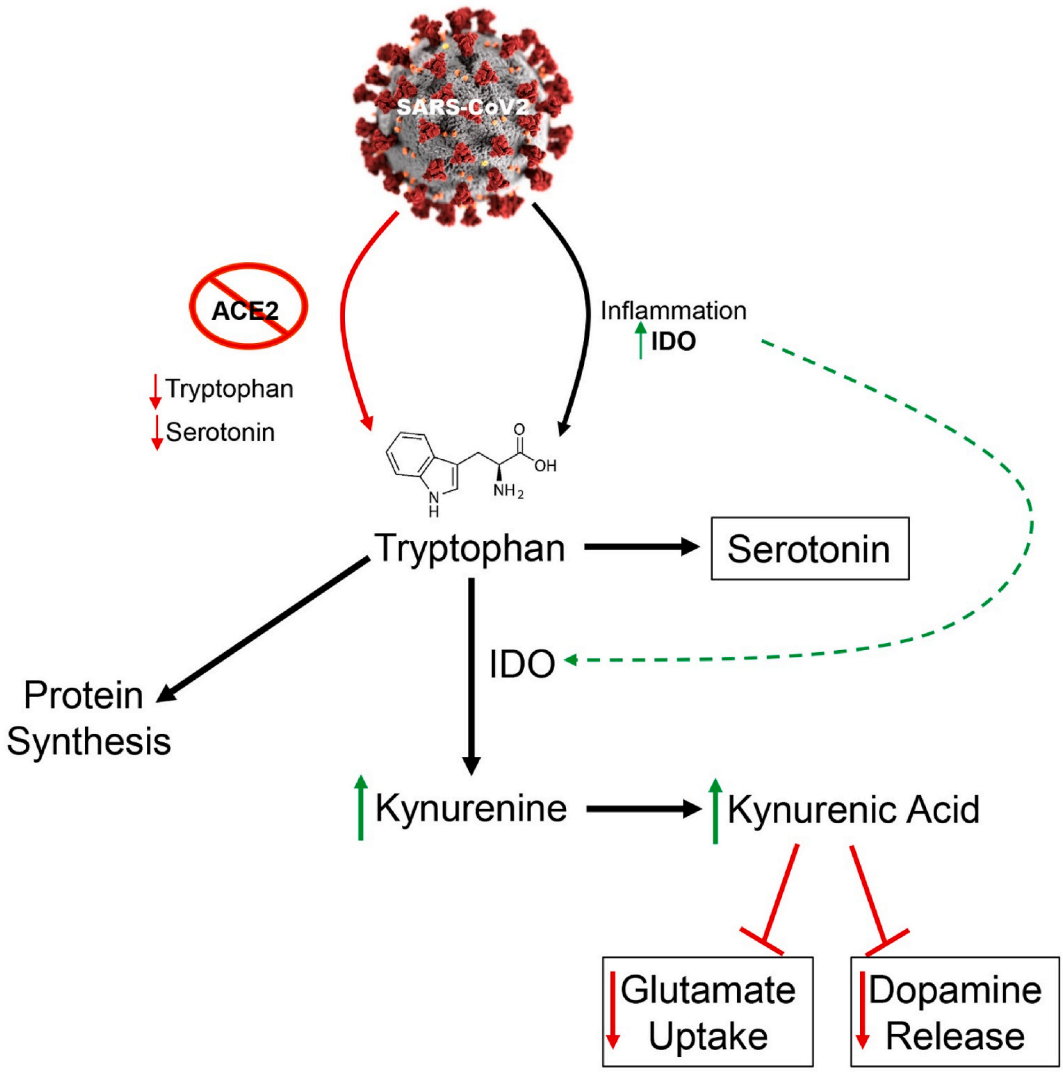
3.1. SARS-CoV2 host factors and kynurenine pathway

The amino acid protein L-tryptophan is an essential amino acid precursor for the biosynthesis of the small endogenous molecules serotonin and melatonin as well as for numerous important CNS and immune system proteins. The kynurenine pathway is a major route of degradation of ingested *l*-tryptophan not used for protein synthesis which accounts for ~95% of the dietary tryptophan disposal (Yu et al., 1999). During tryptophan degradation, the bioactive compound kynurenic acid is produced and accounts for diverse biological functions, including regulation of the immune responsivity and involvement in immune-mediated disorders (Huang et al., 2020b). Several viral infections, including human immunodeficiency virus (HIV) (Huengsberg et al., 1998), hepatitis C virus (HCV) (Larrea et al., 2007), and herpes simplex virus (HSV) (Atlas et al., 2013) increase activation of the kynurenine pathway, which interestingly is implicated in the neurological and cognitive impairments of HIV, HCV, and HSV patients (Atlas et al., 2013; Baran et al., 2012; Weinstein et al., 2019). Therefore, it is possible that the kynurenine pathway is a driving factor in the development of Covid-19 neurological sequelae given that the kynurenine pathway is activated in patients with Covid-19. In two separate metabolomic studies, Covid-19 patients had significantly reduced serum levels of tryptophan and serotonin and elevated serum levels of L-kynurenine (Shen et al., 2020; Thomas et al., 2020). In another study, severely ill Covid-19 patients showed significantly higher L-kynurenine levels compared to Covid-19 negative or control patients (Fraser et al., 2020). These studies did not evaluate CNS levels of kynurenine or kynurenic acid; however, transgenic mice devoid of ACE2, which binds the SARS-CoV2 spike protein, uptake less tryptophan from the gut compared to their wild-type controls (Schwarcz, 2016; Singer et al., 2012) and exhibit significantly lower levels of serotonin in blood and brain (Klempin et al., 2018), implicating ACE2 as modulator in serotonin synthesis. The dopamine synthetic pathway also engages ACE2 mechanisms (Attademo and Bernardini, 2021). Employing a multi-experiment matrix web tool that utilizes microarray datasets to merge information from different datasets and mine for co-expression, dopa decarboxylase (DDC), an enzyme which converts l-3,4-dihydroxyphenylalanine (L-DOPA) into dopamine and l-5-hydroxytryptophan into serotonin, exhibits the highest statistically significant co-expression link with ACE2 (Nataf, 2020). These findings suggest an association between ACE2 function and dopamine/serotonin synthesis by DDC.

Kynurenic acid, a product of L-tryptophan metabolism, also inhibits dopamine release and reduces extracellular dopamine levels in the rat striatum (Borland and Michael, 2004; Wu et al., 2007). This is in part through kynurenic acid-induced antagonism of glutamate receptors and therefore kynurenic acid is also considered a major regulator of glutamatergic activity in the CNS strongly linking the kynurenine pathway to glutamate imbalance (Borland and Michael, 2004; Meier et al., 2016). Alleviating kynurenic acid accumulation in the CNS is thought to positively impact mental health (Wu et al., 2007). Although kynurenine, or its pathway metabolites have not been measured in the CNS of Covid-19 patients, cumulatively, these finding suggest the potential importance of ACE2-kynurenine interactions with serotonin, dopamine, and glutamate systems in normal brain function, and implicates kynurenine dysregulation in the neuropsychiatric and neurological consequences associated with Covid-19.

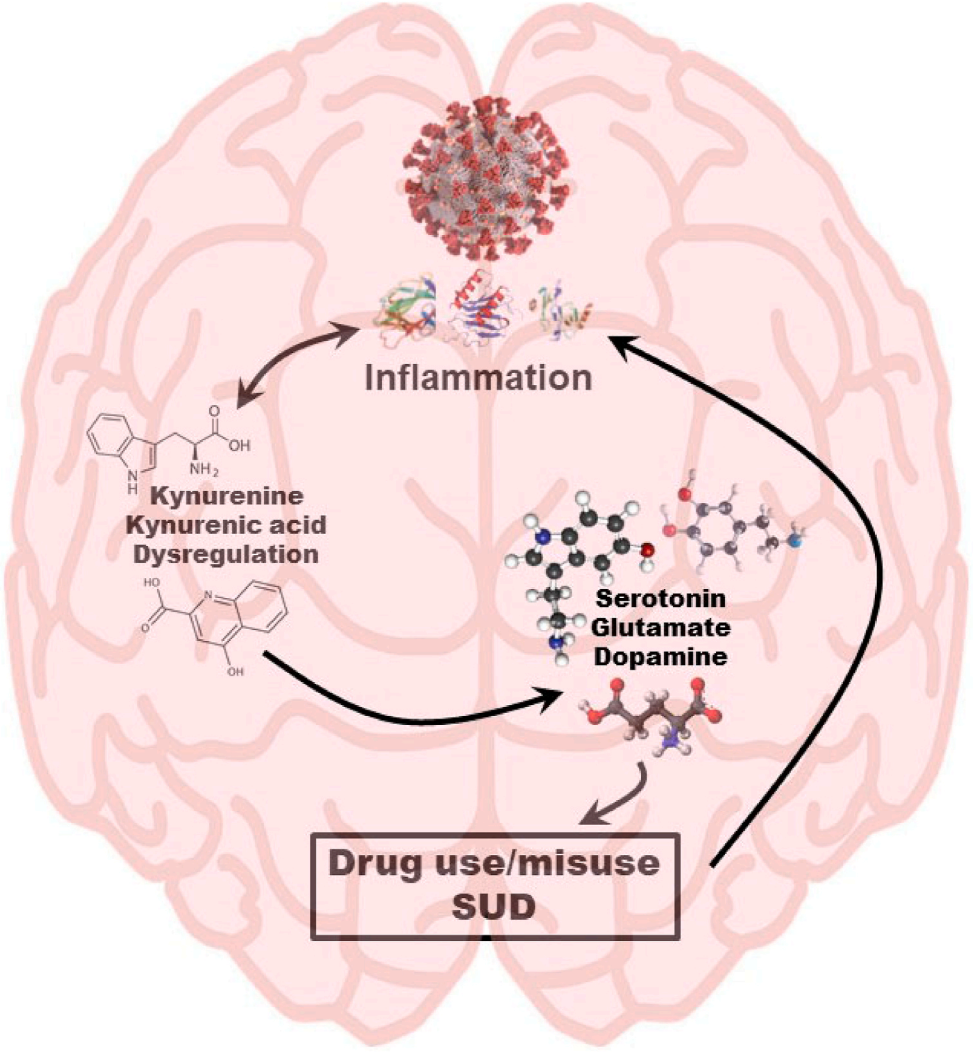
3.2. 3.2 The immune-kynurenine pathway

The bidirectional relationship between innate immunity and the kynurenine pathway provides further evidence for the potential progression of neuropsychiatric disorders during and following recovery from Covid-19. For example, immune signaling, like that induced by Covid-19, impacts downstream metabolism of the kynurenine pathway,



Schematic 2. SARS-CoV2 host factors and inflammation in the regulation serotonin, dopamine, and glutamate. We propose that SARS-CoV2 may activate host factors and increase peripheral levels of inflammatory cytokines and chemokines with the potential to reduce tryptophan and serotonin functionality while kynurenine is increased in Covid-19 patients. With increased IDO activity upon Covid-19-evoked inflammation, tryptophan metabolism may be diverted from maintaining serotonin function into increased levels of kynurenine and kynurenic acid. Given that kynurenic acid antagonizes glutamate receptors and increases glutamate concentrations, excitotoxicity may become a challenge. Kynurenic acid also inhibits dopamine release thereby reducing dopamine levels in the brain.

including quinolinic and kynurenic acid and the neurotransmitters serotonin, dopamine, and glutamate (Bonaccorso et al., 2002; Capuron and Miller, 2011; Maes et al., 2002). Inflammation stimulates the activity and expression of the enzyme indoleamine dioxygenase (**IDO**) which metabolizes tryptophan to kynurenine rather than to serotonin (Badawy, 2017; Kiank et al., 2010; O'Connor et al., 2009; Yisireyili et al., 2018), decreasing the availability of the primary amino acid precursor for the synthesis of serotonin, setting the stage for the disorders mediated by the serotonin system, including the cascade into depression which is resistant to treatment with selective serotonin reuptake inhibitors (for review) (Roman and Irwin, 2020). Preclinical studies demonstrate that a lipopolysaccharide (**LPS**) challenge which activates the immune system, increases IDO activity and expression (Dobos et al., 2012) which likely activates the metabolism of L-tryptophan to kynurenine, initiating an excitotoxic imbalance, based on the strong link of kynurenine to glutamate dysregulation (Borland and Michael, 2004; Meier et al., 2016). Decreased levels of tryptophan and serotonin and increased levels of kynurenine were correlated to levels of IL-6 in Covid-19 patients and associated inflammation (Thomas et al., 2020). Similarly, several studies observed reduced levels of tryptophan and serotonin and elevated levels of L-kynurenine in serum collected from Covid-19 patients (Shen et al., 2020; Thomas et al., 2020), likely *via* increased IDO activity dictated by inflammatory cytokines and chemokines generated during infection with SARS-CoV2. In line with these studies, patients suffering from HCV-induced cognitive impairments, have increased IDO expression in liver and peripheral monocytes, and increased blood levels of kynurenine that correlate to cognitive dysfunction (Larrea et al., 2007; Schulz et al., 2015; Weinstein et al., 2019). Moreover, patients suffering from HIV-associated dementia had increased IDO activity when compared to HIV patients without dementia (Sardar and Reynolds, 1995). In preclinical studies, HIV significantly increase extracellular glutamate concentrations in an *in vitro* astrocyte model that corresponds to clinical studies demonstrating increased excitotoxicity in patients suffering from HIV-associated neurocognitive disorders (Cisneros and Ghorpade, 2014; Cisneros et al., 2020; Fields et al., 2013). Although, IDO levels and activity have not been measured in Covid-19 patients, it is likely that triggering of the immune system by SARS-CoV2 increases IDO activity and kynurenine levels thereby decreasing serotonin and dopamine levels and increasing glutamate excitotoxicity in Covid-19. Thus, dysregulation of the host



Schematic 3. Covid-19 and SUD vulnerability. SARS-CoV2, the virus that causes Covid-19, enters the CNS and activates immune responses, increasing inflammation. The interplay between inflammation and dysregulation of the kynurenine pathway destabilize monoamines including serotonin, glutamate and dopamine, resulting in the increased vulnerability to drug use, misuse, and SUDs.

factor ACE2, inflammation, and altered synthesis and levels of serotonin, dopamine, and glutamate *via* the kynurenine pathway, during Covid-19 is strongly related to neurological sequalae (Schematic 2).

4. Inflammation in SUDs

Glutamate, dopamine, and serotonin crosstalk with the immune system and maladaptive changes induced by inflammation may certainly contribute to increased vulnerability to SUDs, although direct and clear experimental designs for definitive studies are difficult to develop. For instance, TNF-α and IL-1β, classical proinflammatory cytokines, inhibit glutamate uptake in astrocytes and increase ionotropic glutamate receptor expression at the synapse (Cisneros and Ghorpade, 2012, 2014; Cisneros et al., 2020; Olmos and Lladó, 2014; Pickering et al., 2005) and activating glutamate transporters in glial cells reduces cocaine and methamphetamine induced CPP and significantly decreases cocaine self-administration (Nakagawa et al., 2005; Northcutt et al., 2015). Reduced clearance and increased levels of synaptic glutamate is a central mechanism underlying SUD pathophysiology and associated cocaine- and heroin-seeking behaviors. *In vitro*, *in vivo*, and *ex vivo* studies demonstrate that proinflammatory cytokines, including IL-1β, TNF-α, and downstream signaling pathways that include p38 mitogen-activated protein kinase (**MAPK**) and nuclear factor kappa B (**NF-κB**) can modulate the functional activity of serotonin, which is involved in the transition to compulsive drug use behaviors (Bubar and Cunningham, 2006; Cunningham and Anastasio, 2014; Howell and Cunningham, 2015; Müller and Homberg, 2015; Nic Dhonnchadha and Cunningham, 2008; Schwamborn et al., 2016; Steiner et al., 2008; Walsh and Cunningham, 1997; Zhu et al., 2010). Chronic inflammation is characterized to decrease dopamine levels in the CNS which aligns with a similar observation for chronic drug use (Lacagnina et al., 2017; Treadway et al., 2019), supporting the interactive relationship between these system in control of SUD behaviors and implications for CNS mechanisms underlying drug reward (Di Chiara, 2002).

Substances of abuse additionally dysregulate immune signaling driving the complexity associated with understanding maladaptive changes that increase vulnerability to SUDs. Although both TNF-α and IL-1β, cytokines that modulate the activity of serotonin, dopamine, and glutamate, are canonically increased during viral infections, such as HIV (Chivero et al., 2017; Vartak-Sharma et al., 2014) and Covid-19 (McElvaney et al., 2020; Zhang et al., 2020), substances of abuse can also regulate activity of these cyokines. For instance, inflammatory cytokines and chemokines are increased and decreased following exposure to cocaine (Atluri et al., 2016; Kovalevich et al., 2015; Montesinos et al., 2020; Souza et al., 2021), methamphetamine (Karimi-Haghighi et al., 2020; Kays and Yamamoto, 2019; Wang et al., 2018; Yang et al., 2020b)

and/or alcohol (Barr et al., 2016; Crews et al., 2006) and dysregulated following opioid exposure (Cisneros and Cunningham, 2021; Ezeomah et al., 2020). For example, we demonstrated increased and decreased inflammation in the nucleus accumbens relative to the hippocampus in rats withdrawn from chronic self-administration of the opioid fentanyl; these outcomes positively correlated to expression of specific host pattern recognition receptors that trigger inflammatory cascades (Cisneros and Cunningham, 2021; Ezeomah et al., 2020). An unanswered question remains as to the impact of such drug-induced inflammatory changes to perpetuate fentanyl self-administration; if this is the case, there may be the potential anti-inflammatory therapeutics to help mitigate continuing opioid abuse. For instance, opiate antagonists which are used to treat alcohol and opiate use disorders also block induction of innate immune cytokine and chemokine generation, and prevent LPS-induced immune responses (Liu et al., 2000a, 2000b). Perhaps, prevention of inflammatory cytokine and chemokine cascades may reduce alcohol and opiate use. Although statistical significance was not achieved, the TNF-α inhibitor pentoxifylline tended to decrease cocaine use in clinical studies conducted in cocaine-dependent individuals relative to placebo (Ciraulo et al., 2005). Further studies are also required to evaluate whether the immune-kynurenine pathway is directly involved in mediating inflammation evoked by cocaine or other abused drugs. Based on the evidence presented, we speculate that inflammation-induced dysregulation of serotonin, dopamine and glutamate may trigger interacting aspects of underlying the pathophysiology of SUDs and compulsive drug-seeking behaviors (Koob et al., 2014; Koob and Volkow, 2016). Taken together, inflammation and its relationship to this pathophysiology of SUD development and maintenance is undoubtedly complex and worthy of further investigation.

5. Conclusion: Covid-19 and SUD vulnerability

SARS-CoV2, the virus that causes Covid-19, activates the host immune system, thereby impacting the onset of neurological sequelae. The severity of neuropsychiatric and neurocognitive symptoms of Covid-19 are directly associated with the levels of circulating inflammatory cytokines and chemokines (Huang et al., 2020a; Ludlow et al., 2016). Based on the evidence presented in this review, we suspect that inflammation in the CNS, initiated by host immune responses to SARS-CoV2, results in dysregulation in tryptophan metabolism, dually triggered by IDO activity and ACE2 functionality. Increased levels of peripheral kynurenine and CNS kynurenic acid are predicted to destabilize normal serotonin, dopamine and glutamate function vital for normal brain functioning. Alterations in these neurotransmitters are strongly related to drug use and misuse and the vulnerability to develop SUD (Schematic 3). More research is needed to further dissect (1) the CNS inflammatory response to Covid-19; (2) the causal relationship of the immune-kynurenine pathway with Covid-19 neurological sequalae; (3) the impact of Covid-19-related inflammation on IDO activity and interruption of serotonin, dopamine and glutamate metabolism; (4) the role of Covid-19 CNS inflammation in the evolution of drug misuse and SUD; and (5) the regulation of CNS-expressed Covid-19 host factors (e.g., ACE2, TMPRSS2/3, CTSL, NRP-1, TPCN2) following exposure to drugs of abuse and how impaired host factors contribute to sustained clinical challenges during recovery. In summary, as the research field continues to explore these questions and the Covid-19 pandemic continues, we hope that gains in knowledge will frame the means through which we can mitigate suffering of those co-morbid for SUDs and the sequela of Covid-19. The identification of specific targets related to SARS-CoV2-induced inflammation may help guide novel therapeutics approaches to alleviate the future SUD burdens.

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