Coronavirus Disease 2019 (COVID-19) and its neuroinvasive capacity: Is it time for melatonin?

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Abstract

The world faces an exceptional new public health concern caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), subsequently termed the coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). Although the clinical symptoms mostly have been characterized, the scientific community still doesn´t know how SARS-CoV-2 successfully reaches and spread throughout the central nervous system (CNS) inducing brain damage. The recent detection of SARS CoV-2 in the cerebrospinal fluid (CSF) and in frontal lobe sections from postmortem examination have confirmed the presence of the virus in neural tissue. Here, we discuss the COVID-19 outbreak in a neuroinvasiveness context and suggest the therapeutic use of high doses of melatonin, which may favorably modulate the immune response and neuroinflammation caused by SARS-CoV-2. However, clinical trials elucidating the efficacy of melatonin in the prevention and clinical management in the COVID-19 patients should be actively encouraged.

Abbreviations

ACE2: Angiotensin-converting enzyme 2 receptor

α7nAChR: Alpha 7 acetylcholine nicotinic receptor

Ca^{2+}/CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II

CaM: Calmodulin

IKK: I-KappaB-alpha kinase complex

IL-1β: Interleukin 1β

IL-6: Interleukin 6

JAK2: Janus kinase 2

MT1/MT2: Melatonin receptor subtypes 1 and 2

NF-κβ: Nuclear factor kappa-light-chain-enhancer of activated B cells

NLRP3: NLR pyrin domain containing 3

ROS: Reactive oxygen species

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

STAT3: Signal transducers and activators of transcription

TLR: Toll like receptor

TMPRSS2: Transmembrane serine protease 2

TNF-α: Tumor necrosis factor-α

TNFR: TNF receptor

TRADD: TNF receptor-associated death domain

TRAF2: TNF receptor-associated factor-2

1. Introduction

In late December 2019, a number of 27 people with clinical symptoms of dry cough, dyspnea, fever, and bilateral lung infiltrates on imaging with an unknown cause were diagnosed in Wuhan, Hubei Province, China. A few days later, a new virus of great global public health concern was isolated and designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), later referred to as coronavirus disease-2019 (COVID-19) (Chen et al., 2020). This new virus was found to be highly contagious and quickly spread globally, leading the World Health Organization (WHO) to officially declare the COVID-19 outbreak a global pandemic on March 11, 2020 (Mahase, 2020). As an emerging acute respiratory infectious disease, clinical symptoms are characterized predominantly by fever and dry cough followed by dyspnea, bilateral infiltrates, sputum production, haemoptysis, lymphopenia, shortness of breath, sore throat, neurological and gastrointestinal manifestations (Huang et al., 2020; Wang et al., 2020). COVID-19 employs cell receptor angiotensin-converting enzyme 2 (ACE2) for host cell entry (Xu et al., 2020; Zhou et al., 2020), which is present in the type II alveolar cells (Zou et al., 2020), enterocytes from ileum and colon (Xiao et al., 2020), liver cholangiocytes (Qi et al., 2020), aqueous humor (Holappa et al., 2015), myocardial cells (Donoghue et al., 2000), proximal tubule kidney cells (Zou et al., 2020), urothelial bladder cells (Zou et al., 2020), epithelial cells of the oral mucosa (Xu et al., 2020), as well as neurons and glia in the brain stem and particular cerebral regions (Xia & Lazartigues, 2010). The high expression and wide distribution of ACE2 receptor in human body may sustain the ubiquitous potential infection of COVID-19 and explain its tropism. It is also recognized that COVID-19 could be transmitted via multiple routes, predominantly binding to ACE2 alveolar epithelial cells (Wan et al., 2020; Zhou et al., 2020) or by oral-fecal transmission (Gu et al., 2020), among others. To date, it is accepted that the incubation period of COVID-19 is up to 14 days, although it has been suggested that it may be extended up to 24 days, which possibly reflects a double exposure. Furthermore, asymptomatic infection has been additionally reported (Huang et al., 2020; Linton et al., 2020). Interestingly, previous studies showed that the coronavirus also infects the central nervous system (CNS) (Arbour et al., 2000; Lau et al., 2004) since it can spread from the respiratory tract to the CNS, showing neuroinvasive capacities.

There is uncertainty about extra-pulmonary manifestations of COVID-19, including those affecting the CNS. Numerous efforts to implement effective therapeutic strategies are underway. The distressing scenario that the world is experiencing regarding COVID-19 calls for new treatment approaches and, in this respect, we want to emphasize the advantages of melatonin (N -acetyl-5-methoxytrytamine) as a potential therapeutic agent to ameliorate the CNS damage associated with SARS-CoV-2's disease. Melatonin is not a molecule addressed to diminish the viral load nor target specific enzymes involved in viral replication and transcription, nevertheless it has multiple indirect anti-viral actions (Anderson et al., 2015; Elmahallawy et al., 2015; Junaid et al., 2020; Montiel et al., 2015; Tan et al., 2014). In this regard, two recent reviews have suggested the utility of melatonin as adjunctive or even regular therapy for COVID-19 patients who suffer pneumonia, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Tan & Hardeland, 2020; Zhang et al., 2020). Regarding the experimental clinical use of melatonin in the current critical situation, it is important to highlight that melatonin is not only a well-known anti-inflammatory (Carrascal et al., 2018),

anti-oxidative (Rodriguez et al., 2004), and immune-enhancing agent (Carrillo-Vico et al., 2005) but also a molecule with a high safety profile (Seabra et al., 2000). Its small size and amphiphilic nature allow melatonin high cell diffusion capability and it has high permeability through biological compartments, including blood brain barrier (BBB) (Tarocco et al., 2019), reaching cytosolic, mitochondrial, and nuclear compartments (Menendez-Pelaez & Reiter, 1993; Reiter et al., 2020b). BBB integrity is crucial for the maintenance of CNS and thus several neurological disorders debut after deterioration of the BBB (Rosenberg, 2012). Melatonin restores BBB homeostasis limiting microvascular hyperpermeability (Alluri et al., 2016; Liu et al., 2017) and therefore making it a promising candidate against neuroinvasion caused by COVID-19. In view of all above information, this review focuses on characteristics, mechanisms, and implications of CNS involvement caused by SARS-CoV-2 infection, and we speculate how the use of the melatonin could become a basis for a possible neurotherapeutic approach.

2. How does SARS-CoV-2 neuroinvasiveness occur? Melatonin potential to respond to COVID-19 neuropathogenesis

SARS-CoV-2 shares its clinical symptoms with those described for SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV) betacoronaviruses. Previously, it has been reported the presence of SARS-CoV and MERS-CoV particles in the brain of experimental animal models and patients and (Ding et al., 2004; Li et al., 2016; Xu et al., 2005). However, regarding SARS-CoV-2 two important questions that arises are: *i*) The exact route by which the virus enters the CNS and*ii*) whether its the presence may be detected in the cerebrospinal fluid (CSF) or postmortem tissue specimens collected from COVID-19 victims. It is known that human coronaviruses can penetrate the CNS through different routes, directly from the external environment affecting the olfactory nerve and olfactory bulb neuroepithelium or using either the lymphatic or the hematogenous route, which represents an excellent opportunity to infect endothelial cells of the BBB (Desforges et al., 2014). It has been recently reported that human ACE2 receptors are the gateway for SARS-CoV-2 and that transmembrane protease serine 2 (TMPRSS2) is essential for the SARS-CoV-2´s spike (S) protein activation, which facilitates viral attachment to the surface of target cells (Hoffmann et al., 2020). Consequently, it can be thought that those brain regions with the highest expression of ACE2 receptors could turn out to be more affected by SARS-CoV-2 infection, although the involvement of other receptors or co-receptors is not definitely discarded. In this context, a recent study using mRNA expression levels data provided by the Allen Human Brain Atlas has demonstrated ACE2 in brain regions, such as olfactory bulb (OB) (Lapina et al., 2020). This may explain the neuropathogenic impact of SARS-CoV-2 on the partial loss of the sense of smell or total anosmia, as a result of nasal inflammation, mucosal edema, and obstruction of airflow into the olfactory cleft. Additionally, the analyses of three databases have shown high expression levels of human ACE2 in regions of the human brain (e.g., substantia nigra) and both neurons and astrocytes, which would help us to understand how SARS-CoV-2 can spread into the brain and cause neurological damage (Chen et al., 2020) (Figure 1). Conversely, OB imaging by magnetic resonance was found normal in a COVID-19 patient with anosmia and without intensity signal of nasal congestion in the early phase of the disease (Galougahi et al., 2020); even though, anosmia may persist for a long time. Another essential point for initial viral neuroinvasion is the recent announcement by genome sequencing of the first reported case of SARS-CoV-2 in the CSF (Xiang, 2020). Additionally, a recent case study reporting viral particles in endothelial cells and frontal lobe sections obtained at forensic examination confirmed the presence of SARS-CoV-2 in neural tissue (Paniz-Mondolfi et al., 2020). After these observations, brain infection is being seriously considered by the scientific community because important pathologies at neurological level are emerging associated with COVID-19 patients; encephalopathy (Filatov et al., 2020; Poyiadji et al.), meningitis/encephalitis (Moriguchi et al., 2020; Ye et al., 2020), Guillain-Barré syndrome (Zhao et al., 2020), cerebrovascular disease (Helms et al., 2020; Li et al., 2020; Wu et al., 2020) and epilepsy (Karimi et al., 2020). Moreover, Li and colleagues (Li et al., 2020) have hypothesized that the ability of SARS-CoV-2 targeting the CNS may, at least in part, explain the acute respiratory failure of COVID-19 patients. Conversely, it has been argued that the brain dysfunction induced by SARS-CoV-2 still lacks strong evidence and, therefore, this relevant question should be further investigated.

Taken together, the abovementioned evidence indicates that counteracting or mitigating the neuroinvasion of

SARS-CoV-2 emerges as an essential strategy to prevent or treat COVID-19. At this point is where melatonin can act as a protective agent against virus-related diseases (Anderson & Reiter, 2020; Elmahallawy et al., 2015; Silvestri & Rossi, 2013; Tan et al., 2014) and several pathologies of CNS ((Brigo et al., 2016; Farez et al., 2015; Gerber et al., 2005; Ramos et al., 2017) including those affecting BBB (Ramos et al., 2017) (Figure 1). Regardless, is it possible that melatonin acts inside the neural cells targeted by SARS-CoV-2. Its amphiphilic nature helps it to reach intracellular organelles, binding to mitochondrial and cell cytosol proteins, increasing, thus, its neural availability (Tan, 2010) and therapeutic versatility in at least three different ways. Firstly, melatonin binds to calmodulin (CaM) and may act on the Ca^{2+}/calmodulin-dependent protein kinase II (Ca^{2+}/CaMKII) system, thereby regulating the expression of ACE2 (Lambert et al., 2008). Secondly, CaMKII has been found to copurify with proteasomes of the brain (Bingol et al., 2010) and the ubiquitin-proteasome system is involved in the early viral replicative cycle. Interestingly, like a proteasome inhibitor (Vriend & Reiter, 2014), melatonin may regulate several events involved in proteostasis, through the Ca^{2+}/CaMKII system, which can also influence SARS-CoV-2 infectivity. Thirdly, given its tectonic impact in host cell homeostasis, it is expected that SARS-CoV-2 dysregulates mitochondrial metabolism. In this regard, it is worth noting that many of the actions displayed by melatonin are directed to maintain mitochondrial function. Therefore, any decrease of melatonin (pineal or mitochondrial) levels may open a way for depleting the viral control of cellular metabolism and thus slowing down the replication of SARS-CoV-2 (Anderson & Reiter, 2020).

About 10-15% of the COVID-19 patients with ARDS and organ failure have been associated with the commonly known as hyperinflammation or "cytokine storm syndrome". The question that arises is; might SARS-CoV-2 infection trigger a cytokine storm in the brain? In light of recent COVID-19-associated case reports describing a rare form of severe brain damage with hemophagocytic lymphohistiocytosis (HLH) (Radmanesh et al., 2020), and a patient with an acute necrotizing hemorrhagic encephalopathy (Poyiadji et al., 2020), it should be considered that COVID-19 infection may induce a "cytokine storm syndrome" in the brain (Mehta et al., 2020), deserving special consideration and further research. In agreement with the above, it has also been reported that up-regulation of proinflammatory mediators and a deregulated immune response can be useful predictors of lethality by COVID-19 (Ruan et al., 2020). Therefore, there are a plethora of alterations at interconnected signaling pathways, such as the mammalian target of rapamycin (mTOR) (Zhou et al., 2020), sirtuins (SIRTs) (Anderson & Reiter, 2020), NLRP3 inflammasome (Deftereos et al., 2020), Toll Like Receptors (TLRs) (Conti et al., 2020) or single-pass type I transmembrane receptor (Notch) (Rizzo et al., 2020) are key factors that may modulate COVID-19-related cellular and molecular events (Figure 2). In this context, as an universal regulator targeting a large number of different signaling pathways and physiological processes, melatonin may exerts a significant neuroimmunomodulatory protection against viral infections (Liu et al., 2019; Ma et al., 2018; Shukla et al., 2019; Tiong et al., 2019; Xu et al., 2018). Therefore, the capacity of the indoleamine for counteracting the neuroinvasion by SARS-CoV-2-infection cannot be underestimated, nor neglected and unquestionably requires further research.

3. Melatonin receptors in the context of CNS involvement for SARS-CoV-2

Given the astonishing pleiotropy of melatonin, it may be expected that cellular and molecular mechanisms by which this indoleamine mediates neuroprotection would be complex as well. To a some extent the biological effects of melatonin are mediated through the interaction with two high-affinity G protein-coupled receptors, MT1 and MT2, which are involved in multiple signaling cascades in cell protection and survival (Liu et al., 2016). Both in the CNS and peripheral organs melatonin receptors are ubiquitously distributed (Ekmekcioglu, 2006; Ng et al., 2017). Unfortunately, we must assume our current ignorance of the mechanisms by which MT1 and MT2 may influence melatonin-mediated signaling in the brain of patients afflicted by COVID-19. However, melatonin receptor-mediated protection has already been suggested against lethal viral diseases such as the Venezuelan equine encephalomyelitis (VEE) virus (Valero et al., 2009) or to improve the total antioxidative defense capacity against respiratory syncytial virus (RSV) (Huang et al., 2010). Moreover, it has been reported that 1/3 patients with confirmed COVID-19 present acute cerebrovascular disease and epilepsy, among other neurological symptoms (Jin et al., 2020). It is also known that COVID-19 patients might develop a "cytokine storm syndrome" due to an exacerbated level of pro-inflammatory

biomarkers which contribute to significantly increase the risk of ischemic stroke. SARS-CoV-2 may enter the CNS via the haematogenous diffusion and infect the endothelial cells of the BBB. In this context, melatonin may elicit part of its neuroprotective effect through melatonin receptors, thus MT2 up-regulation would not only preserve BBB integrity but also attenuate the activation of astrocytes and microglia (Lee et al., 2010).

In Wuhan, a case of epilepsy in a COVID-19 patient was reported (Mao et al., 2020). Indeed, down-regulation of the hippocampal MT2 receptor conferred protection against seizures and exhibited the anticonvulsant activity of melatonin (Stewart & Leung, 2005). Additionally, T lymphocytes seem to be more vulnerable against SARS-CoV-2 infection through S protein and CD147 (Wang et al., 2020), an extracellular matrix metalloproteinase inducer of the proinflammatory cytokine cyclophilin A, secreted by monocytes/macrophages and endothelial cells. T lymphocytes express both melatonin receptors, MT1 and MT2 (Pozo et al., 2004; Slominski et al., 2012), and in this regard, in the infected T cells melatonin may; *i*) regulate the immunostimulatory activity mediated by MT1 and MT2 and *ii*) block cyclophilin A/CD147 signaling pathway (Su et al., 2016). For these reasons, in the search for new pharmacological strategies against COVID-19, we focused our attention on the exogenous supplementation with melatonin to preserve the immune response and counteract the neuroinflammation through its widely distributed receptors in the CNS and most of the immune cell.

4. Understanding of COVID-19's long-term impact on the CNS and the influence of melatonin as a preventive agent

All countries are suffering the scourge of COVID-19. Unfortunately, science is still learning the natural history and pathogenicity of this emerging coronavirus as well as its immediate and devastating effects on human health. We should ask ourselves, what will be the long-term consequences of COVID-19? Lippi and co-workers (Lippi et al., 2020) have proposed the possibility that months or years after infection several tissues, including the brain, patients may suffer an accelerated aging, which could manifest in neurodegenerative disorders such as Parkinson disease. Something that seems epidemiologically proven is that the most susceptible people to SARS-CoV-2 infection are the middle-aged and elderly. Based on this clinical evidence, we hypothesize that, at least partially, the progressive melatonin decline with age may account for the apparent increased COVID-19 sensitivity over life-span and specially in the elderly. As a consequence of aging, the pineal gland accumulates calcium deposits and both serum and CSF melatonin release decreases (Reiter et al., 1981; Reiter et al., 2014), which is being increasingly related with numerous dysfunctions and pathophysiological changes (Karasek, 2004). The involvement of melatonin in the context of neurodegeneration is promising since it has been well documented to counteract most of the physiopathological events that trigger neurodegenerative disorders (Ramos et al., 2020). Interestingly, a certain relationship between nicotinic acetylcholine receptors (nAChRs) and infectivity by SARS-CoV-2 is suspected. However, this raises the controversy about whether it is a facilitating effect because nicotine would promote SARS-CoV-2 cell penetration through nAChRs up-regulation (nAChRs) (Kabbani & Olds, 2020) or the opposite by the low prevalence of smokers among COVID-19 people in China (Guan et al., 2020) or the hypothesized competition of nicotine and SARS-CoV-2 for binding nAChR (Changeux et al., 2020). Thereby, a putative role of nAChRs in the modulation of ACE2 has been suggested at cardiovascular level (Oakes et al., 2018) and presently it should be considered a possible interplay between both ACE2 and overexpressed nAChRs in the context of the SARS-CoV-2 neurotropism and neuroinfection. At this point, melatonin becomes relevant by the modulation of neuroinflammation (Niranjan et al., 2012) and oxidative stress (Parada et al., 2014) via alpha 7 acetylcholine nicotinic receptor (α7nAChR) which oligomers are among the most frequent in the brain (Gotti & Clementi, 2004) and mediate many of the beneficial actions of the indoleamine including mitochondrial regulation. It is also important to note that the COVID-19 may impact on the neurotransmission process. Nataf (Nataf, 2020) using a multiexperiment matrix showed a significant co-expression link between ACE2 and Dopa Decarboxylase (DDC), which may explain that any SARS-CoV-2-induced downregulation of ACE2 expression, previously reported for SARS-CoV (Kuba et al., 2005), might disrupt the dopamine and serotonin synthesis pathway, with the subsequent reduction of these neurotransmitters in blood and brain as well as the serotonin-dependent melatonin availability. This hypothesis should be corroborated and correlated in COVID-19 patients affected by generalized anxiety disorder and depressive symptoms (Huang

& Zhao, 2020).

5. Melatonin supplementation against SARS-CoV-2 neurotropism: Dosage and safety

To our knowledge, melatonin has not yet been tested in COVID-19 patients. Nevertheless, determining the safety and the precise doses of this molecule to prescribe are challenges to be fulfilled. When orally administered, melatonin has a low and variable bioavailability ranging into 3-33 % (Andersen et al., 2016c; Di et al., 1997; Harpsoe et al., 2015). Moreover, brain is the organ where melatonin reaches lower concentration after its administration, which could justify the use of higher doses to counteract the neuroinvasive potential of SARS-CoV-2 (Andersen et al., 2016b). In this regard, a new melatonin galenic formulation with a higher bioavailability and faster absorption through the CNS would be required, such as intravenous (IV) (Peschechera & Veronesi, 2020) or intranasal administration (García-García et al., 2016; Zetner et al., 2016).

Even though there are not sufficient short- or long-term studies with exogenous melatonin focused on clarifying clinical safety (Seabra et al., 2000), a significant number of studies indicate that the melatonin is safe, even at doses 100 times higher than physiological concentrations (Andersen et al., 2016a; Andersen et al., 2016b; Brzezinski, 1997; Nickkholgh et al., 2011). Then, what are the recommended melatonin dosing regimens in COVID-19 patients? The answer would depend on the administration route and formulation. Reiter et al. (Reiter et al., 2020a) have recently proposed a dose of 40 mg/day orally to control the spread of the disease. In this context, we hypothesized for COVID-19 patients in hyperinflammation phase, an oral dose of 100 mg/day or at least 1 mg/kg b.w would be required to establish whether melatonin inhibits the neuro-impact of SARS-CoV-2, especially among patients with severe neurological pathologies.

Melatonin co-administration with other drugs is also an attractive strategy to improve the management of patients with COVID-19 and to reduce the possible drug side effects. The potential of melatonin as an adjuvant treatment (Zhang et al., 2020), as well as its combination with mercaptopurine (Zhou et al., 2020) had been suggested as a feasible therapy against SARS-CoV-2.

Since the effective vaccine and antiviral drugs are unavailable, it is critically important to look for an alternative strategy for COVID-19 treatment. To this aim, melatonin is a serious candidate to consider because it shows a low toxicity risk, the pharmacological efficacy needed for the preventive treatment of COVID-19 infection and it has several clinical actions from which COVID-19 patients could benefit. It is time, therefore, to translate the therapeutic capacities of melatonin for the improvement of clinical practice and protection of public health in the current COVID-19 outbreak.

6. Concluding remarks

The current SARS-CoV-2 pandemic has stressed the public health systems until unprecedented limits. The socio-economic consequences are expected to be terrible worldwide and, most important, a health threat has spread across the planet. Faced with this panorama, people are reacting with panic to SARS-CoV-2 infection since several issues need solving.*i*) The mechanisms associated with the infectiousness of SARS-CoV-2 is not clear and their elucidation is urgently needed*ii*) SARS-CoV-2 causes different symptoms in different people and a biological explanation is lacing. *iii*) Clinicians are still unsure whether people infected with COVID-19 can be reinfected;*iv*) The lack of effective vaccines and specific antiviral drugs targeted at SARS-CoV-2 which makes it difficult for treating or controlling the pandemic. And *v*) what will the long-term health consequences of affected COVID-19 patients be? Given the panorama of such an uncertain future facing us at the present time, we emphasize that further investigation in the treatment with melatonin is urgently required, as well as that clinical trials are strongly needed for the best understanding of the impact of its administration in patients affected by COVID-19.

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Competing Interests' Statement:

The authors declare no conflict of interest.

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Legend to figures

Figure 1. The nasal cavity could be the gateway of SARS-CoV-2 to reach directly the central nervous system through and affecting the olfactory nerve and olfactory bulb neuroepithelium. Once in the brain SARS-CoV-2 would initiate the innate immune responses at early stages of the COVID-19 resulting in neurological disorders. At this point, high doses of melatonin may exert anti-inflammatory effects and acting as a buffer against enhanced immunoreactivity, which would reduce the neuropathogenesis of SARS-CoV-2 infection.

Figure 2. Hypothetical diagram of the possible targets where melatonin may act against SARS-CoV-2 infection in the CNS. SARS-CoV-2 enters neuronal cells through ACE2, as the receptor binding domain, and TMPRSS2 for spike protein (s-protein) priming. Next, SARS-CoV-2 nucleocapsid triggers clathrin-mediated endocytosis enhancing cytoplasm release. Subsequently, the single negative strand RNA [(-)gRNA] synthesized from (+)gRNA template is used to replicate more copies of viral RNAs. Afterwards, subgenomic RNAs (sgRNAs) synthesized from the (+)gRNA template encode viral structural and accessory proteins, which are assembled with newly synthesized viral RNAs to form new virions. Then, virus particles are transported in secretory vesicles to the plasma membrane and released by exocytosis. Furthermore, the entry of SARS-CoV-2 into neuronal cells may dysregulate mitochondrial metabolism increasing ROS and leading to the induction of endoplasmic reticulum stress. In this regard, melatonin's high diffusibility allows it to enter in neuronal cells, it binds to CaM and may act on the Ca^{2+}/CaMKII system, regulating the expression of ACE2, modulating the linking between endoplasmic reticulum stress and inflammatory response and scavenging ROS. However, in both MT1/MT2 and α7nAChR receptors, melatonin-mediated signaling may influence in reduced SARS-CoV-2 entry. When SARS-CoV-2 infects the CNS, it triggers the release of pro-inflammatory cytokines. i) TNF-α, which acts by binding to TNFR receptor recruiting TRADD. This protein binds to TRAF2 to phosphorylate and activate the IKK. Then, IKK complex phosphorylates IKBα, resulting in the translocation of NF-κβ to the nucleus, where it targets many coding genes for mediators of inflammatory responses. ii) IL-6 induces gene activation in response to cytokine receptor stimulation. STAT3 proteins dimerize and translocate to the nucleus. JAK2/STAT3 signaling is a crucial link acting as a pivotal mediator of neuroinflammation. iii) The binding of SARS-CoV-2 to the TLR (TLR3/7/9) up-regulates the proinflammatory transcription factor NF-κβ and causes the release of pro-IL-1β which is cleaved by caspase-1, followed by NLRP3 inflammasome activation. Consequently, melatonin may revert these pro-inflammatory effects by inhibiting the JAK2/STAT3 signaling pathway and NF-κβ translocation. In addition, as an anti-inflammatory agent, melatonin inhibits the activation of NLRP3 inflammasome. Stimulation (blue colored) or inhibition (red colored) by melatonin and SARS-CoV-2 are also shown.