Virus-Induced Neuropathogenesis

Subjects: Clinical Neurology

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Viral infections may cause neurological disorders by directly inducing oxidative stress and interrupting immune system function, both of which contribute to neuronal death. Several reports have described the neurological manifestations in Covid-19 patients where, in severe cases of the infection, brain inflammation and encephalitis are common. Recently, extensive research-based studies have revealed and acknowledged the clinical and preventive roles of melatonin in some viral diseases. Melatonin has been shown to have antiviral properties against several viral infections which are accompanied by neurological symptoms. The beneficial properties of melatonin relate to its properties as a potent antioxidant, anti-inflammatory, and immunoregulatory molecule and its neuroprotective effects.

Keywords: Virus-Induced Neuropathogenesis ; Melatonin

1. Introduction

Neurodegenerative diseases are incurable and affect millions of people worldwide, leaving the individuals with debilitating health conditions. Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative diseases. Neurodegenerative diseases are progressive in nature and lead to degeneration and nerve cell death, ultimately causing a decline in both the central nervous (CNS) and peripheral nervous system (PNS) functions. Accumulation of intracellular misfolded and fibrillated proteins are major hallmarks of such diseases and involve the specific actions of endoplasmic reticulum (ER) stress, ubiquitin proteasome system (UPS), and phagosomes. Mutations in the mitochondrial DNA induce reactive oxygen species (ROS) production, leading to oxidative stress. Upregulation of the apoptotic signaling via the caspase cascade drives the progression of cell death [1].

Melatonin is a neurohormone produced in and secreted by the pineal gland, especially at night. It reaches the cerebrospinal fluid (CSF) either indirectly after its release into the blood and it subsequent discharge into the third ventricle, or, more likely, by being secreted directly into the ventricle by the pinealocytes [2], from where it reaches the cerebral tissues under physiological conditions, as evidenced by in vivo scintigraphy and autoradiography [3]; from the CSF, melatonin can more readily diffuse into the neural tissue where it protect neurons and glia from damage [4]. Melatonin is also likely produced in neurons and glial cells, which may contribute to the high levels of melatonin in the CSF compared to blood concentrations. Considering these findings, CSF-derived melatonin may decelerate the progression of neurodegenerative diseases [4]. Melatonin has a wide range of neuroprotective actions by modulating the pathophysiological mechanisms and signaling pathways observed in neurodegenerative diseases [5][6]. Along with its antioxidant, immunomodulatory, anti-inflammatory, and anti-apoptotic properties, melatonin also regulates abnormal protein dynamics, mitochondrial dysfunction and altered bioenergetics [7].

It is well documented that viral infections can lead to neurodegenerative changes, causing significant brain damage, along with neurobehavioral alterations. Viruses have evolved through their ability, over time, to impact the CNS by crossing the blood–brain barrier (BBB), leading to neuronal deficits and degeneration. The relationship between viral infections and brain disease dates back to 1385, when the link between psychosis and influenza infection was established, which became more apparent during the Spanish flu epidemic in 1918 [8] and perhaps more evident when a condition encephalitis lethargica was recognized viral antigens in the brains of infected people [9]. Additional evidence was provided when rats exposed to Japanese encephalitis virus (JEV) developed symptoms of PD [10]. Moreover, studies in infectious CNS disorders further revealed that viruses such as herpes and measles probably breach oligodendrocytes and compromise the immune system activity by altering normal cellular physiology, resulting in the demyelination of neurons, as observed in multiple sclerosis, in sclerosing panencephalitis and in neuromyelitis optica, which are chronic autoimmune demyelinating diseases [11]. Additionally, potential links have been established between herpes simplex virus (associated with APOE-e4 allele) [12][13] and cytomegalovirus infection with inflammatory responses [14]. As human immunodeficiency virus (HIV) infection compromises the immune system, affected individuals become more susceptible to infections and diseases such as in HIV encephalopathy, a viral infection that causes neurodegenerative changes which are attributed to its ability to exploit the BBB, leading to dementia, which corresponds to the rate of spread of infection along with

remarkable amyloid plaque formation [15]; this increases the risk of developing AD. Regarding PD, as the basal ganglia is an assailable target of HIV, infected subjects have a greater risk of developing this devastating condition [16]. In this context, apart from neurodegenerative diseases, much information is currently being gathered on investigations into the preventive roles of melatonin in patients affected by viral diseases like Covid-19 [17][18][19][20][21][22].

2. Therapeutic Role of Melatonin on Post Infection Complications of Viral Induced Neuropathogenesis

2.1. Melatonin and Anosmia

Olfactory sensitivity exhibits a diurnal rhythm and the presence of melatonin receptor mRNAs and melatonin synthesis enzymes in the olfactory bulb affirms the possibility that melatonin is locally synthesized in the olfactory bulb [23]. Melatonin is widely known to inhibit neuronal apoptosis. In the olfactory bulb mucosae of rats, melatonin decreased the activity of caspase-3 and BAX and upregulated the expression of BCL-2, which is known to inhibit apoptosis by preserving the integrity of the mitochondrial membrane and which also inactivates BAX and other pro-apoptotic proteins [24]. Rodent studies have pointed out that GABAergic cells stimulate the production of interferons are essential for odor detection, where these cells exert a tonic inhibition that regulates the sensitivity of odor perception, as demonstrated in the mammalian brain [25]. Interestingly, modulation of the GABAergic system by melatonin might suggest the presence of a pathway for the neuroprotective effects of melatonin, given that melatonin impacts the circadian rhythm of endogenous GABAergic mechanisms [26][27]. Some anesthetic studies in humans have indicated a correlation between the levels of serum melatonin and olfactory identification impairment [28], which substantiates the involvement of melatonin in anosmia-like conditions.

2.2. Melatonin and Myelination

A study in a rodent model inoculated by the neuro-adapted John Howard Mueller (JHM) strain of mouse hepatitis virus (JHMV) has shown the development of an acute encephalomyelitis which disseminates throughout the brain parenchyma, causing demyelination and chronic neuroinflammation. The T cell chemoattractant chemokine CXCL10 (interferon-inducible protein IP-10) serves to recruit activated T and B lymphocytes expressing CXC chemokine receptor 3 (CXCR3), the receptor for CXCL10. Investigations have revealed that CXCL10 expression in the CNS is responsible for regulation of the JHMV viral replication and its uninterrupted expression leads to demyelination through CD4+ T-cell-induced enhancement of neuroinflammation via IFN-γ-mediated expression of other chemokines [29]. In this context, it has been reported that melatonin is involved in the regulation of CXCL10 production [30]. Melatonin also inhibits demyelination and increases remyelination, suggesting its local regulation in white matter astrocytes by serotonin availability and apolipoprotein E4 [31]. Melatonin stimulates oligodendroglia-enhanced remyelination by increasing pyruvate dehydrogenase kinases 4 (PDK4) expression and N-acetylaspartate (NAA) levels with a simultaneous reduction in inflammatory mediators in a mouse model of multiple sclerosis [32]. Moreover, multiple sclerosis is a chronic, progressive, inflammatory autoimmune disease of the myelin sheath. It has been recently documented that melatonin displays neuroprotective effects during both remyelination and demyelination stages in a rodent model of multiple sclerosis [33].

2.3. Melatonin and Myalgia

Myalgias are defined as muscle aches presenting as a sharp sporadic ache or a constant and deep ache. They are common in patients exposed to viral infections like coronaviruses and influenza. Nearly 30–40% of Covid-19 patients display myalgia as an early symptom [34][35]. The common underlying pathogenic mechanisms include oxidative stress and inflammation. In general, melatonin availability has been significantly associated with increased muscle strength in the average elderly population [36]. The results of one study confirmed the beneficial effects of melatonin in age-related muscle weakness [37]. Melatonin, received in a dose- and time-dependent manner, also reduced fibromyalgia-related musculoskeletal damage. Nonetheless, the therapeutic benefits of melatonin have not been thoroughly evaluated in several pain syndromes like fibromyalgia, headaches and chronic back pain [38].

2.4. Melatonin and Hypoxic Ischemia/Stroke

Hypoxic-ischemia often causes serious brain damage. Accumulating evidence has suggested that the neuroimaging features of hospitalized Covid-19 patients are usually dominated by acute ischemic infarction and intracranial hemorrhages [39]. Areas of the brain which may be preferentially affected by hypoxic-ischemic encephalopathy include the cerebral cortex, watershed regions between the anterior and middle cerebral artery and middle and posterior cerebral artery territories, basal ganglia, hippocampi, thalamus, cerebellum, and deep white matter [40]. Melatonin may potentially be useful in the treatment of neurodegenerative conditions that may involve free radical production, such as perinatal

hypoxia. In this particular experiment, exogenously administered melatonin in animals effectively protected against brain injury by oxidative stress [41]. Increasing evidence has shown that, in animal stroke models, administering melatonin significantly reduces infarct volume, edema, and oxidative damage and improves electrophysiological and behavioral performance. Melatonin has shown neuroprotection in cerebral ischemia in acute, sub-acute, as well as chronic stages. In addition to its potent antioxidant properties, melatonin exerts antiapoptotic, antiexcitotoxic, anti-inflammatory effects and promotes mitochondrial functions in animals with cerebral ischemia [42]. Furthermore, in a neonatal rat model of stroke, melatonin increased myelin basic protein immunoreactivity in the cingulum along with increment in the mature oligodendrocytes, thus promoting myelination in the white matter with a subsequent reduction in inflammation [43]. Melatonin regulates the immunogenic cascade and inflammatory signaling in ischemic damage to the brain induced by stroke [44]. Clinical investigation in stroke patients revealed the therapeutic efficacy of melatonin administration by reduction in the oxidative response and increase in the survival rate of the patients in the intervention groups [45].

2.5. Melatonin and Prion Diseases

Viral infections can lead to prion diseases, which are pathological conditions associated with neuronal damage and associated behavioral disorders. Melatonin significantly alleviated PrP^c induced apoptosis and mitochondrial fragmentation and dysfunction, prevented the suppression of ATP and reduced the overproduction of ROS in N2A cell cultures, thus alleviating neuronal damage [46], which is suggestive of melatonin's use in the treatment of prion diseases. Sleep disruption is a prevalent clinical feature in many neurodegenerative disorders, including human prion diseases. Fatal familial insomnia (FFI) is an inherited prion disease that mainly affects the thalamus. The thalamus is the part of the brain that controls the sleep–wake cycle, but is also known as the "relay center" of the brain because it helps the different parts of the brain communicate with each other [47]. A decrease in the levels of serum melatonin and corresponding disturbances in sleep patterns are observed in FFI patients [48]. Based on this information, it can be speculated that a planned timely daily dose of melatonin might improve sleep parameters in such patients.

2.6. Melatonin and Guillain–Barré Syndrome

Several reports have described Covid-19 patients as suffering from GBS [49]. GBS is triggered by a viral or bacterial infection where the body's own immune system attacks the nerves. Symptoms start as weakness and tingling in the feet and legs that spreads to the upper body, and later, paralysis can also occur. GBS has several forms; of them, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common, in which muscle weakness starts in the lower part of the body and spreads upward. Miller Fisher syndrome (MFS), in which paralysis starts in the eyes, and acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN), are less common forms. Sleep and psychiatric disturbances, along with anxiety, are common manifestations of GBS [50]. As such, low-level inflammation induced by neurotropic viruses increase the risk of psychiatric disorders [51]. Additionally, neuropathic pain also accounts for the neurological complication associated with this disorder [52]. It has been shown in preclinical studies that melatonin may be useful in the management of neuropathic pain [53]. Disturbances in the melatonin secretion is a characteristic feature in many psychiatric disorders [54] and exogenous melatonin has proven useful in patients with varied forms of psychiatric disturbances [55].

2.7. Melatonin and Neurotransmitters

Virus-induced pathogenesis also involves glutamate dysfunction, leading to brain damage [56]. Human coronavirus strain OC43 affects human glial and neuronal cells. Expression of the glial glutamate transporter 1 is responsible for glutamate homeostasis, which has been shown to decrease following this viral infection. One report demonstrated that inhibition of glutamate excitotoxicity using a 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propranoic acid (AMPA) receptor antagonist (GYKI-52466) improved clinical scores related to paralysis and motor disabilities in S mutant virus-infected mice, as well as protecting the CNS from neuronal dysfunctions [51]. Melatonin has dynamic neuroprotective properties. In an HT22 mouse hippocampal cell line, melatonin reduced glutamate-induced oxytosis via its antioxidant action targeted at the mitochondria [57]. Recently, targeting glutamate with melatonin has been discussed for its possible therapeutic benefits in the treatment of anxiety [58], which is yet another complication observed in virus-infected patients.

Viruses such as wild type vesicular stomatitis virus (VSV) can rapidly and selectively infect and destroy serotonin neurons in young mice and rats. A subsequent immune system-mediated response eliminates all trace of the virus from the brain, leaving a permanent reduction in serotonin neurons, with consequent behavioral alterations [59], with no viral element remaining. The neurotransmitter and behavioral changes resulting from this initial infection may last for the lifetime of the organism, despite the lack of any trace of the virus in the brain, and with little detectable viral-mediated neuropathology evident by standard screening methods at the end of life. In this context, it has been shown that melatonin regulates (via its deacetylation to 5-methoxytryptamine) CYP2D-mediated synthesis of serotonin from 5-methoxytryptamine in the brain

regions; hippocampus, cortex, striatum, nucleus accumbens, hypothalamus and thalamus as well as the medulla oblongata and cerebellum of the male Wistar rat, which are well recognized as the targeted pharmacological action of melatonin [60].

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