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Amantadine Treatment for Parkinson's Disease during COVID-19: Bimodal Action Targeting Viral Replication and the NMDA Receptor

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Abstract

Parkinson's Disease [PD] and COVID-19 share common features that include age dependency and their association with co-morbidities such as cardiovascular disease, diabetes and respiratory problems. Shortness of breath [dyspnea] is a feature of both conditions. Symptoms of PD are known to deteriorate during systemic infections and common features of COVID-19 [fever, delirium, stress] may aggravate tremor, gait and dyskinesias in PD. Parkinsonism is a feature of many viral encephalatides with associated basal ganglia neuropathology. Following uptake from the circulation or via the upper nasal transcribial route, the spike protein of SARS-CoV-2 binds to a host cell protein ACE2 expressed on neurons and neuroglia. Essential host cell proteases such as Cathepsin L [CTSL] then cleave the spike protein leading to fusion of viral and host cell membranes and release of the viral genome into the host cell. Cryo-microscopic studies confirm that SARS-CoV-2 binds with high affinity to ACE2. High throughput drug screen gene expression analysis of 466 agents with the potential to down-regulate expression of CTSL identified amantadine which ranked 5th in efficacy. A link between viral infection and treatment of PD by amantadine started serendipitously with the report of a PD patient noting improvement of tremor and rigidity after treatment with amantadine for influenza A infection. Amantadine's beneficial action in PD relates to its ability to indirectly replenish dopaminergic activity via stimulation of the NMDA subclass of ionotropic glutamate receptors. An NMDA receptor antagonist was effective in limiting viral replication with improvement of neurological symptoms due to infection with HCoV-OC43. The ability of amantadine to exert beneficial effects in COVID-19 is worthy of clinical investigation.

Abbreviations

ACE2: Angiotensin Converting Enzyme-2; COVID-19: Coronavirus Disease-2019; CSF: Cerebrospinal Fluid, CNS: Central Nervous System; Cryo-EM: Cryo-Electron Microscopy; CTSL: Cathepsin L; HCoV: Human Coronavirus; MHV: Mouse Hepatitis Virus; NMDA: N-methyl D-aspartate; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; SARS: Severe Acute Respiratory Syndrome; US-FDA: United States Food and Drug Administration

Introduction

The severe acute respiratory syndrome Coronavirus-2 [SARS-CoV-2] targets multiple organs including the brain resulting in a wide spectrum of neurological conditions. In a retrospective study from Wuhan, China, neurological manifestations associated with COVID-19 were reviewed in 214 hospitalized patients with laboratory-confirmed diagnosis of SARS-CoV-2 infection [1]. 78 patients [36.4%] manifested neurological symptoms including acute cerebrovascular disease, ataxia, seizure, dizziness, headache, impaired levels of consciousness and skeletal muscle injury. Neurological symptoms were also reported following a study of 58 patients with SARS-CoV-2 infection where over 80% manifested symptoms of encephalopathy, agitation, confusion and corticospinal tract signs [2]. Although the presence of neurological disorders is not included in the WHO [2020] list of co-morbidities associated with high risk of severe illness from COVID-19, there is evidence to suggest that the presence of such disorders is strongly associated with poor outcome in infected patients [3].

The SARS-CoV-2 genome encodes approximately 25 key proteins required by the virus in its bid to infect humans and to replicate. The virus starts by gaining access to the CNS from the circulation or via the upper nasal transcribial route allowing access to the brain or peripheral nerve terminals [4]. Then, in common with many other coronaviruses, the now notorious "spike protein" of SARS-CoV-2 starts its journey by binding to a host cell membrane receptor known as Angiotensin Converting Enzyme-2 [ACE2]. Brain expresses ACE2 receptors on both neuronal and glial elements in many regions of the brain including cardio-respiratory centres in the medulla and it has been suggested that the neuro-invasive potential of the SARS-CoV-2 virus plays a role in the acute respiratory failure characteristic of COVID-19 [5,6]. Following binding of the spike protein to the ACE2 receptor on the host cell membrane activation of host cell proteins such as Cathepsin L [CTSL] occurs resulting in cleavage of the viral spike protein that (Figure 1), in turn, leads to the fusion of viral and host cell membranes and release of the viral genome into the cytoplasm of the host cell [7]. Cryo-Microscopic [Cryo-EM] determination of the SARS-CoV-2 spike confirms that the virus binds to ACE2 and does so with higher affinity compared to previous SARS viruses [8].

Disruption of CTSL has the potential to provide the basis for COVID-19 therapy and this can occur as the result of decreased expression of CTSL, by inhibition of CTSL enzyme activity or by

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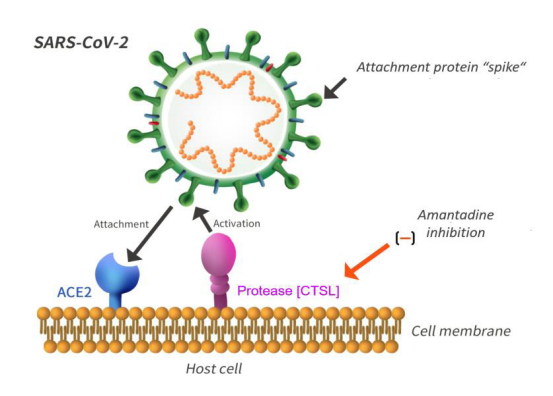

Figure 1: The schematic representation depicts the molecular steps involving key proteins during invasion of the host cell by SARS-CoV-2.An initial step involves the binding of the SARS-CoV-2 spike with high affinity to the host cell membrane protein ACE2, a type 1 membrane protein expressed in lung, heart, kidney and brain. This is followed by cleavage by host cell proteins, a key step for viral activation and infection. In the case of SARS-CoV-2, use is made of the endosomal cysteine protease Cathepsin L [CTSL]. This process results in fusion of the viral and host cell membranes followed by release of the viral genome into the cytoplasm of the host cell. Amantadine has the potential to disrupt the process by down-regulation of the CTSL gene leading to impaired viral replication.

disruption of CTSL environment resulting from, for example, increases of pH in the lyposomes [7]. High throughput drug screen gene expression analysis of 466 agents with the potential to down-regulate expression of CTSL identified amantadine which ranked 5th in efficacy. Moreover, since amantadine is also an established lysosomotropic alkalinizing agent, the possibility of disruption of lysosomal pH changes was entertained. A number of key lysosomal pathway genes were found to be down-regulated. Together, these findings strongly suggest that the mechanism of action of amantadine is the consequence of its ability to down-regulate CTSL gene expression coupled with disruption of the CTSL environment caused by increased lysosomal pH. These mechanisms have the potential to protect against viral entry and, ultimately, viral replication [7].

Parkinson's Disease [PD] in the COVID-19 era

PD and COVID-19 share common features including the age dependency of the two conditions as well as their association with serious comorbidities such as cardiovascular disease, diabetes and respiratory difficulties [9]. These observations have drawn attention to issues relating to the effects of COVID-19 on PD severity, possible long-term sequelae and effects related to PD care [10]. Conversely, concerns have been raised relating to the effects of PD on immune status leading to the possible increased susceptibility of PD patients to COVID-19 [11]. It is well known that PD symptoms may deteriorate during systemic infections leading to symptoms ranging from mild worsening to frank akinetic crisis [12]. Fever is a common diagnostic symptom in COVID-19 and it has been reported that delirium and fever may result in subacute motor deterioration in PD [13]. Moreover, the combination of fever and altered dopaminergic medication intake has been known to predispose PD patients to the parkinsonism/hyperpyrexia syndrome, a movement disorder emergency [14]. Other features of COVID-19 such as stress, fear and anxiety are known to aggravate tremor, gait and dyskinesias as in PD [15] and may compromise the efficacy of L-Dopa [16].

Enhanced antibody responses to a range of coronaviruses have been reported in the CSF of PD patients and there is substantial evidence to suggest that parkinsonism is a feature of several viral encephalatides with associated PD-type regional neuropathology [17]. In this latter regard, substantia nigra is known to be susceptible to damage from H1N1 influenza virus and the coronavirus MHV-A59 exhibits selective affinity for basal ganglia resulting in marked postural and locomotor deficits associated with neuronal cell death and marked gliosis in substantia nigra [18,19]. SARS-CoV-2 has been detected in the CSF of two patients with meningitis/encephalitis and a case of acute necrotizing encephalopathy associated with cytokine storm in COVID-19 has also been reported [20-22]. A viral etiology [in whole or in part] for PD raises again the subject of "post-encephalitic parkinsonism", a term introduced following the 1918 pandemic influenza outbreak where the chronic phase of parkinsonism occurred at various times post-exposure from immediate to several years or even a decade later [23].

In a study of a cohort of 153 non-demented PD patients without history of heart or lung diseases, shortness of breath [dyspnea] was observed in 39.2% of cases accompanied by significantly higher United Parkinson Disease Rating Scale [UPDRS] scores [24]. It is likely that the sub-group of PD patients with dyspnea would be at elevated risk of severe respiratory failure following infection by SARS-CoV-2.

Amantadine to the rescue?

The link between amantadine, viral infection and PD started with the serendipitous observation reported by a 68-year old woman with moderate-severe PD who, upon taking amantadine for the management of symptoms of influenza, noted a remarkable remission in her cogwheel rigidity and tremor; the symptoms reappeared upon cessation of amantadine. One year later, a clinical trial was conducted in 163 PD patients treated with amantadine in which the majority showed significant clinical benefit [25]. Amantadine went on to receive FDA approval for the treatment of Influenza A. In 2013, using a robust yeast growth restoration assay together with a sensitive high throughput screen for the search for inhibitors of the M2 channel of the influenza virus, 21 active compounds were identified out of 250,000 chemicals and natural products screened; amantadine was one of the 21 compounds [26].

Investigations of the beneficial effects of amantadine against other viruses have continued apace. Human coronaviruses are established respiratory pathogens possessed with neuro-invasive and neurotropic properties. A report published in 2007 described conductance and binding of amantadine to a pore formed by a lysine-flanked trans membrane domain of the SARS coronavirus [SARS-CoV] envelope [E] protein [27]. A subsequent report described the results of studies of the neuro-invasive human respiratory coronavirus HCoV-OC43, a strain known to infect human neural cells where it activates neuroinflammatory and neurodegenerative processes leading to paralytic disease and motor dysfunctions in virus-infected mice [28]. Treatment with meantime, a structural analogue of amantadine resulted not only in attenuation of mortality rates in infected animals; the treatment also reduced HCoV-OC43 replication in the CNS in a dose-dependent manner. Both, memantine and amantadine are potent non-competitive antagonists of the N-Methyl-D-Aspartate

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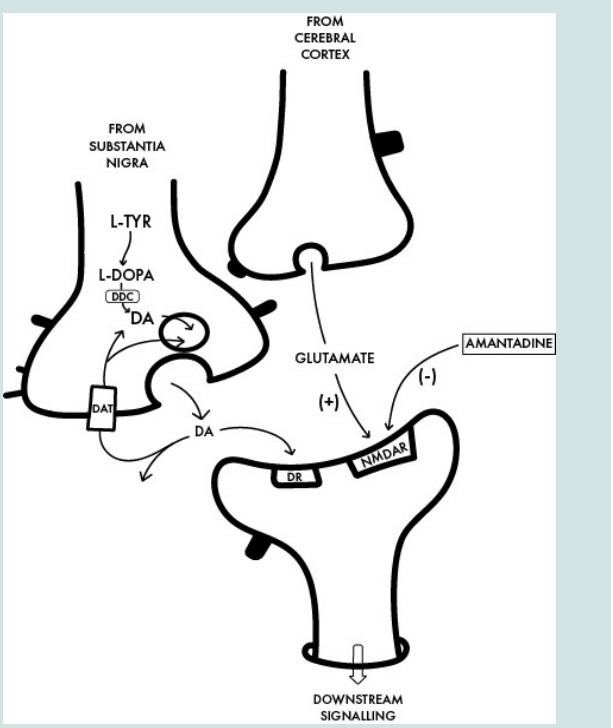

Figure 2: Interface between a dopaminergic [DAergic] nigrostriatal nerve terminal in which DA is synthetized from L-Tyrosine [L-TYR] via L-DOPA to DA with a glutamatergic terminal of the cortico-striatal tract and the post-synaptic neuron. The benefit of amantadine for the treatment of the motor disturbances in PD is attributed to its non-competitive antagonist action on the post-synaptic NMDA receptor [NMDAR] resulting in the restoration of the balance between nigrostriatal and corticostriatal inputs in favour of increased net production of DA. DDC: Dopa Decarboxylase [enzyme for DA synthesis], DAT: Dopamine Transporter [DA reuptake], DR: Post-Synaptic DA Receptor.

[NMDA] subclass of ionotropic glutamate receptors in the brain (Figure 2). Over-activation of these receptors may result in excitotoxicity mediated by neural Ca^{2+} overload leading to neuronal cell death, a mechanism that has been implicated in the pathogenesis of neurodegenerative diseases including PD.

Amantadine is widely used for the treatment of the motor symptoms of PD and for the control of L-Dopa-induced dyskinesias [29]. The mechanism of action is predicated on its NMDA receptor-antagonist action and there is preliminary evidence of a protective effect of amantadine in relation to COVID-19 in a study of 5 PD patients (Figure 2), all receiving L-Dopa, all having tested positive for SARS-CoV-2 by RT-PCR. None of the 5 PD patients went on to develop clinical symptoms of COVID-19 and motor function was unaffected [30]. Given the suggested beneficial effects of amantadine and possibly other members of the adamantane group of compounds against coronaviruses, repeated appeals have been made for the repurposing of these agents for the treatment of COVID-19 [31].

Conclusions and Future Prospects

The review focuses on the cerebral consequences of COVID-19 in the light of the current pandemic that, at the time of submission of this manuscript had infected over 10 million people worldwide with attendant fatality rate in excess of 500,000. In addition to patient age and of comorbidities such as cardiovascular disease, diabetes and respiratory disorders it may now be appropriate for the presence of chronic neurological disorders be included in the high-risk group for severe COVID-19 according to modified WHO guidelines.

Amantadine was approved by US-FDA since 1968 as a prophylactic agent for influenza and more recently for the treatment of PD and its associated dyskinesias. Importantly, in the high throughput screening study in which amantadine was noted to down-regulate the expression of the host-cell protease CTSL, the effective dose of amantadine was within one order of magnitude of the drug's clinical pharmacokinetic profile for the treatment of PD and could therefore conceivably be employed within current labelling guidelines [7]. There is currently very little information relating to side effects of amantadine in the context of COVID-19 therapy; side effects in PD patients treated with amantadine are relatively mild consisting of confusion, blurred vision, foot edema and constipation. Hallucinations have occasionally been described following abrupt discontinuation of amantadine. On a related topic, there is currently no published literature relating to the evolution of resistance to amantadine of the SARS-CoV-2 virus but, in view of the established amantadine resistance in the case of other RNA viruses such as influenza-A, it will be essential that laboratory surveillance be performed in a timely manner [31].

Amantadine has the capacity to interfere with molecular mechanisms implicated in the replication of SARS-CoV-2 resulting in reduced viral load as well as its associated disease severity and progression. Concomitantly, amantadine has the potential, by virtue of its NMDA receptor antagonist action, to restore the dopaminergic deficit in PD (Figure 2). Several appeals have been made for the initiation of appropriate clinical trials on the use of amantadine for the treatment of COVID-19 [31-34].

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