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Potential for the Repurposing of Adamantanes for the Treatment of COVID-19

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Editorial

It is remarkable that, in the relatively short period of time since its appearance on the world stage, numerous reports related to SARS-CoV-2 the virus responsible for COVID-19 appear regularly in the literature. This Special Issue of The Journal of Pharmaceutics and Pharmacology initiated in early June 2020 focuses on the repurposing of adamantanes for their potential use in the prevention and treatment of COVID-19. Adamantanes such as amantadine, rimantadine and the novel spiro adamantane amine represent a large family of tricyclic agents many members of which have proven efficacy against a range of viruses including animal and human corona viruses such as SARS-CoV-1, 229E and HCoV-OC43 [Butterworth].

Proposed mechanisms of action of SARS-CoV-2 fall into one of at least 3 categories all of which are amenable to modification by adamantanes. For example, SARS-CoV-2 contains 4 proteins namely E and M that form part of the viral envelope, N protein that binds to the viral genome and the spike protein [S] that binds to the host cell receptor ACE2. The SARS-CoV-2 viroporin E is implicated in key aspects of the life cycle of the virus and e gene deletion results in up to 1000-fold decrease in viral replication. Molecular docking studies reveal that amantadine interacts with the E channel leading to prevention of release of the viral nucleus into the host cell [Aranda-Abreu et al.]. High throughput drug screen gene expression analysis identified amantadine as a potent lysosomotropic agent and down-regulator of Cathepsin-L a host cell protease involved in the entry of SARS-CoV-2 into the host cell leading to decreased replication, decreased viral load and potentially improved clinical outcome in infected patients. [Smieszek et al.]. Evidence suggests that adamantanes in general and amantadine itself together with its structurally-related agent memantine in particular are potent antagonists of two key transmitter systems namely the glutamate [NMDA] receptor and the nicotinic cholinergic α7nACh receptor. In addition, SARS-CoV-2 is known to enter the host cell via clathrin-mediated endocytosis which is inhibited by the adamantanes amantadine and rimantadine. Adverse effects of smoking on outcomes in COVID-19 have been attributed to the effects of nicotine on the latter receptor. As NMDA antagonists, adamantanes appear to prevent motor disabilities and reduce viral replication of in neuro-invasive human respiratory coronavirus HCov-OC43-infected mice in a dose-dependent manner [Brenner, Butterworth].

Reports relating to possible clinical benefits of adamantanes in the prevention and/or treatment of COVID-19 during the last 6 months are limited to small uncontrolled/observational studies and individual case reports. Many cases of prevention of symptoms of the disease were reported and, surprisingly, benefit was apparent in many cases of older individuals and/or patients with other serious medical conditions. In a typical case, a 57-year-old male patient with Type 2 diabetes [10 yrs duration] tested positive for COVID-19 by RT-PCR treated with amantadine [100 mg/d, 10days] showed improved oxygen saturation and daily activities by day 14 [Aranda-Abreu et al.]. A subsequent review of this and other case reports involving 23 patients with co-morbidities [Type-2 diabetes, Multiple sclerosis, neurological conditions including Parkinson's disease] provided evidence of prevention of the appearance of typical COVID-19-related clinical features of infectious disease following treatment with amantadine or memantine. Appeals were made by many authors for the prompt initiation of randomized controlled trials [Cortes Borra].

Widespread damage to the CNS continues to be documented in COVID-19 patients with symptoms ranging from decreased levels of consciousness to stroke and encephalitis. Alterations of key cellular processes implicated in aging and neurodegeneration also occur. In the final contribution to this Special Issue, evidence for the potential use of amantadine and memantine for the prevention and treatment of the neurological complications of COVID-19 is reviewed [Butterworth].