Perampanel, a novel neuroprotector and antiviral agent in COVID-19?

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Abstract

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A new human coronaviruses (SARS-CoV-2) are the cause of currently severe acute respiratory syndrome (SARS), as occurred in the previous epidemic caused by SARS-CoV-1. Perampanel is a drug currently used in epilepsy, with an innovative mechanism of action, through receptors [2-amino-3- (3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) that modulates the flow of glutamate. It has been reported the utility of another drugs used in neurodegenerative disorders such a memantine. It works through the N-methyl-D-aspartate receptor (NMDA) and regulates the transporting of glutamate. Both are receptor antagonists. Memantine has seen to reduce the symptoms and replication viral in animal models infected with HCoV. We propose that perampanel works in a similar way and may have therapeutic and neuroprotective effects in COVID-19 infection. New studies on it should be started.

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Human coronaviruses (HCoV) as pathogens in upper and lower respiratory tract infections [1] are the cause of severe acute respiratory syndrome (SARS), as occurred in the previous epidemic as a consequence of SARS-CoV-1 [2]. Over the years, HCoV has also been associated with other pathologies such as myocarditis and meningitis [3], [4], as well as, occasionally, acute disseminated encephalitis [5]. SARS-CoV-1 has neuroinvasive properties in mice [6], as does its murine counterpart, the mouse hepatitis virus (VHM), which causes neurodegenerative and neuroinflammatory disease in mice and rats[7] and is used to establish an animal viral model of multiple sclerosis (MS). HCoV have neuroinvasive and neurotropic properties in mice and humans, known to produce respiratory, enteric and neurological infections in various animal species [7]. The HCoV OC43 (SARS-CoV-1) strain causing the previous severe acute respiratory syndrome (SARS) epidemic, can infect and subsist in human neural cells and trigger a neuroinflammatory and neurodegenerative response, such as the production of proinflammatory mediators (tumour necrosis factor alpha [TNF-], interleukin-1 [IL-1])[8].

Thus, it has been described that the current SARS-CoV2 (COVID-19) is a neuroinvasive virus capable of causing a cytokine storm as an inflammatory response, and that it could persist in infected patients [9]. The viral persistence of the Nidovirus (coronavirus) in the CNS has been described by Lavi, E., Schwartz, T., Jin, Y., et al. 1999[10]. Coronaviruses 229E, 293, and OC43 have been isolated in the cerebrospinal fluid and brain of patients with multiple sclerosis [11], and the immune response after infection may be involved in the induction or exacerbation of outbreaks of multiple sclerosis. in susceptible individuals [12]. This would also support the idea that the apparent reinfections of patients with COVID-19 who passed the disease, suffer it again with or without neurological symptoms, due to the persistence of the virus in neurons in a latency state with low replication that remain undetectable with the usual tests. A recent study suggests that the coronavirus may remain in the lungs after patients have recovered [13]. The Nipah virus (a paramyxovirus) causes many of the same neurological symptoms, and reactivation has been observed, months or years later, due to latent infections [14]. Both viruses (COVID-19 and Nipah virus) selectively infect neurons.

Brison E, et al [8] demonstrated that HCoV-OC43 is a neuropathogenic virus in mice causing encephalitis, and that a viral mutant with a single point of mutation in the spike protein of the viral surface (S) leads to a paralytic disease induced by glutamate excitotoxicity. Memantine, an N-methyl-D-aspartate receptor (NMDA) antagonist that regulates glutamate flux, decreases mortality and replication rates of SARS-CoV-1 in the central nervous system in a dose-dependent manner in this model. This could suggest that memantine could act as an antiviral agent while improving neurological symptoms. Here it should be noted that mutations in the SARS-CoV-1 spike (S) protein appear after a sustained infection of cells of the central nervous system, as a possible viral adaptation to the environment [15]. In this sense it has been seen that a single amino acid change can influence the virus-induced neuropathology, modulated by the viral protein S in mice, and producing from encephalitis to a neuropathology characterized by flaccid paralysis [8]. Memantine resulted in improvement of symptoms of this induced neuropathology. From all of the above, it can be speculated that another molecule with an effect similar to NMDA receptor antagonism, with modulation of glutamate levels, such as perampanel, could have the same effects in coronavirus neuroinfection.

Glutamate is an important excitatory neurotransmitter of the central nervous system (CNS) involved in various neurophysiological functions. A disruption of your homeostasis leads to excitotoxicity, a pathological process by which neuronal cells (neurons and glial cells) can be damaged after excessive stimulation of glutamate at its specific ionotropic receptors [2-amino-3- (3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA). Hyperactivation of the AMPA and NMDA receptors may cause a neural

overload of Ca2, which can mediate said excitotoxicity through a cascade of events that involve the production of free radicals, mitochondrial dysfunction and the activation of various enzymes such as phospholipase A2, which damages the cell membranes, the cytoskeleton and DNA [16]. Memantine blocks NMDA receptors only when they are overstimulated by glutamate [17]. On the other hand, perampanel works by selectively blocking AMPA receptors, it has no direct affinity for other metabotropic receptors, such as those of kainate or NMDA, although modulation of AMPA receptors can indirectly modify the activity, expression and location of NMDA receptors, which could mediate the mechanisms of synaptic plasticity and of neuropathology by HCoV. The variant of SARS-CoV-1 that hosts a point mutation in its superficial spike glycoprotein (S) (Y241H) produces glutamate excitotoxicity and has been associated with dysregulation at the level of AMPA receptors [8], whose antagonism is responsible the perampanel.

In addition to neuroinflammation, glutamate excitotoxicity may be involved in CNS infections with West Nile Virus [18], human immunodeficiency virus (HIV) [19], human herpes virus 6 (HHV-6) [20], human T-lymphotropic virus type 1 (HTLV-1) [21], bornavirus [22] and Sindbis virus [23]. Dysregulation of glutamate homeostasis leads to neuronal loss (neurodegeneration) [8], as shown in other virus infections [24]–[26].

Currently, the study by Brison, E., et al. is the first evidence that a glutamatergic transmission modulator shows antiviral properties against a human neurotropic and neuroinvasive virus [8]. Fact not yet studied for the perampanel. This novel mechanism of action of memantine and perampanel could suppose that it worked as an antiviral agent in various neurological diseases with viral involvement, such as herpetic encephalitis or meningitis, and coronavirus infection. And probably with a neuroprotective effect.

For all these reasons, it would be interesting to carry out new studies on the role of perampanel in models of SARS-CoV-1 and SARS-CoV-2 (COVID-19) infection. In the hope of being able to act as therapy for the current or future COVID-19 pandemic.

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