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A Novel Vaccine Employing Non-Replicating Rabies Virus Expressing Chimeric SARS-CoV-2 Spike Protein Domains: Functional Inhibition of Viral/Nicotinic Acetylcholine Receptor Complexes

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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The emergence of the novel β-coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic of coronavirus disease 2019 (COVID-19). Clinical studies have documented that potentially severe neurological symptoms are associated with SARS-CoV-2 infection, thereby suggesting direct CNS penetration by the virus. Prior studies have demonstrated that the destructive neurological effects of rabies virus (RABV) infections are mediated by CNS transport of the virus tightly bound to the nicotinic acetylcholine receptor (nAChR). By comparison, it has been hypothesized that a similar mechanism exists to explain the multiple neurological effects of SARS-CoV-2 via binding to peripheral nAChRs followed by orthograde or retrograde transport into the CNS. Genetic engineering of the RABV has been employed to generate novel vaccines consisting of non-replicating RABV particles expressing chimeric capsid proteins containing human immunodeficiency virus 1 (HIV-1), Middle East respiratory syndrome (MERS-CoV), Ebolavirus, and hepatitis C virus (HCV) sequences. Accordingly, we present a critical discussion that integrates lessons learned from prior RABV research and vaccine development into a working model of a SARS-CoV-2 vaccine that selectively targets and neutralizes CNS penetration of a tightly bound viral nAChR complex.

MeSH Keywords: Coronavirus • COVID-19 • Rabies virus • Receptors, Nicotinic • Vaccines

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Background

The emergence of the novel β-coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic of coronavirus disease 2019 (COVID-19) [1]. Currently, in mid-May 2020, there are over 4,000,000 confirmed cases of COVID-19 and over 300,000 deaths due to COVID-19 worldwide, according to the COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University (*https://coronavirus.jhu.edu/map.html*).

There is now increasing collaborative activity by governments, academic institutions, biotechnology companies, and the pharmaceutical industry to investigate the range of possible treatments for COVID-19 and vaccines to prevent infection from SARS-CoV-2 [1]. Current approaches are drawing on previous studies on severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) [1]. For example, studies have shown that SARS-CoV and SARS-CoV-2 have structural similarities within their respective receptor-binding domains (RBDs) of the S1 spike protein subunit that mediate strong multi-point binding to the extracellular globular domain of angiotensin-converting enzyme-2 (ACE2), which may involve neurological expression [2–9]. Within the lung, widespread expression of ACE2 by alveolar epithelia and capillary cells facilitates viral infection via internalization and replication, leading to severe respiratory disease [2,3]. Recent evidence of co-morbid neurological sequelae of SARS-CoV-2 infection has been reported in the presence or absence of severe respiratory disease where patients have presented with symptoms of nausea, vomiting, anosmia, loss of taste, impaired consciousness, agitation and confusion, corticospinal tract signs, and cerebrovascular diseases, including encephalopathy [5–7].

As discussed below, a significant body of empirical studies has demonstrated that the destructive neurological effects of rabies virus (RABV) infections are mediated by CNS transport of the virus tightly bound to the nicotinic acetylcholine receptor (nAChR). It has also been recently hypothesized that a similar mechanism may exist to explain the multiple neurological effects of SARS-CoV-2 via binding to peripheral nAChRs followed by orthograde or retrograde transport into the CNS [10,11]. Potential portals for transport of SARS-CoV-2/nAChR complexes into the CNS include the olfactory nerve and primary olfactory neurons [9,12], and/or peripheral trigeminal sensory terminal structures located within the olfactory epithelium [13,14]. Further studies are required to fully test the hypothesis that the nAChR receptor represents an obligate biochemical chaperone or effector protein responsible for transport of infective SARS-CoV-2 particles into discrete CNS areas. As a corollary, pharmacological targeting of SARS-CoV-2/nAChR complexes may represent a novel vehicle for prevention and control of neurological comorbidities of COVID-19 infection [10]. There is the potential for new clinical trials to investigate nicotine as a means of blocking SARS-CoV-2-nAChR binding to prevent or treat COVID-19 (*https://www.theguardian.com/world/2020/apr/22/french-study-suggests-smokers-at-lower-risk-of-getting-coronavirus*). As such, we present a critical discussion that integrates lessons learned from prior RABV research and vaccine development into a working model of a SARS-CoV-2 vaccine that selectively targets and neutralizes CNS penetration of a tightly bound viral nAChR complex.

The Case for a Functional Association of SARS-CoV-2-and nAChR in the Pathophysiology of COVID-19

Several empirical studies have demonstrated that the nAChR represents a major receptor for the RABV that mechanistically drives CNS transport of infective viral particles, leading to classic neurological sequelae associated with disease progression [15–17]. Due to the efficient neuroinvasive properties of RABV [18,19], including the ability to bypass the blood-brain barrier, studies have used RABV-based vectors for the delivery of drugs to the CNS, with some success [20]. Furthermore, genetic engineering of the RABV has been employed to generate novel vaccines consisting of non-replicating RABV particles expressing chimeric capsid proteins containing human immunodeficiency virus 1 (HIV-1) [21,22], MERS-CoV, Ebolavirus, and hepatitis C virus (HCV) sequences [23–25].

In light of the above, a similar mechanism may underlie the multiple neurological effects of SARS-CoV-2 infection within the CNS. Patients with COVID-19 commonly present with sensory neurological symptoms that include anosmia and/or loss of taste. It has been proposed that the olfactory epithelium within the nasal cavity represents an early-stage locus for SARS-CoV-2 infection and replication, as reflected by ACE2 expression by a variety of non-neuronal cell types [9], followed by orthograde transport within the primary olfactory pathway into CNS structures [12]. Additionally, CNS entry of SARS-CoV-2/nAChR complexes may involve retrograde transport from peripheral trigeminal sensory terminal structures located within the olfactory epithelium [13,14,26,27]. Interestingly, similar lines of empirical evidence support a mechanism for RABV infection within the CNS via retrograde transport of RABV/nAChR complexes from sensory terminals of trigeminal ganglia [28,29], trigeminal nerve terminals within the olfactory epithelium, or primary olfactory neurons [30].

From a biochemical perspective, a conserved nAChR-binding motif within the primary amino acid sequences of the RABV glycoprotein, HIV-1 gp120, and snake venom neurotoxins has been observed [31–33]. The HIV-1 envelope, gp120, has been

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reported to induce neuropathological changes similar to those in patients with HIV-1-associated neurocognitive disorders and triggers an upregulation of the α7-nAChR [34]. Importantly, snake venom toxins have been demonstrated to be high-affinity competitive antagonists of the nAChR. Sequence analysis of the SARS-CoV-2 spike protein identified homologous regions of 4-5 amino acids with aligned sequences in alpha-bungarotoxin and alpha-cobratoxin, thereby suggesting potential binding affinity and antagonism of the α7-nACh receptor [11]. Sequence homologies between putative nAChR-binding domains within the SARS-CoV-2 spike protein and HIV-1 gp120 have yet to be determined, although there are recent indications for shared CNS comorbidities [35]. In sum, convergent lines of evidence presented here support the potential construction and testing of novel homologous vaccines employing non-replicating RABV particles expressing chimeric capsid proteins containing antigenic sequences from SARS-CoV-2 spike protein and RABV glycoprotein.

Conclusions

Our critical discussion has presented a hypothesis with a potentially high degree of biomedical feasibility, indicating that a novel non-replicating RABV vaccine engineered to contain chimeric capsid proteins with discrete SARS-CoV-2 spike protein domains may represent a highly efficacious preventive measure against neurological comorbidities of COVID 19. This hypothesis is based on critical evaluation of the current biomedical literature. Currently, however, there are no vaccines in development that are designed to specifically target or neutralize SARS-CoV-2 entry into CNS areas. The accepted standard of clinical care employs passive immunization with human rabies immune globulin (HRIG) in conjunction with RABV vaccine administration to prevent animal-to-human transmission of RABV. Positive results obtained from *in vitro* studies designed to evaluate potential inhibitory effects of HRIG on SARS-CoV-2 entry and replication in human neuronal cell lines expressing the nAChR may provide putative proof of principle of our testable hypothesis and justify subsequent human clinical trials. Recent studies in the veterinary literature have described a highly infectious SARS-CoV-like canine respiratory coronavirus (CRCoV) that is a major causative agent in the canine infectious respiratory disease complex [36]. We speculate that the absence of observed neurological sequelae in dogs afflicted with CRCoV may be a functional consequence of widespread prophylactic RABV vaccination that potentially engenders cross-reacting IgGs against viral nAChR-binding domains. Finally, conformational matching and stereo-selective recognition of mammalian protein domains by discrete regions of the SARS-CoV-2 spike protein may have been acquired via evolutionary selection of randomly obtained genomic sequences by multiple recombination events. Evolutionary conservation of multiple amino acid domains within the primary sequences of variant subtypes of the nAChR, which appears to be evolutionarily ancient, may underlie the observed functional targeting by RABV capsid glycoprotein and putatively by SARS-CoV-2 spike protein [37].

Statement

The views expressed here do not represent those of the Library of Congress.

Conflict of interest

None.

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