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Commentary

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Could SARS-CoV-2 Invade the Brain?

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Abstract

COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is highly contagious. Patients with COVID-19 usually have respiratory symptoms such as fever, cough and difficulty in breathing, but also exhibit symptoms such as anosmia/hyposmia, ageusia/dysgeusia, unilateral or bilateral weakness of limbs, altered mentation, seizures etc. owing to complicated or concomitant onset of neurological disorders such as stroke, encephalopathy, meningitis, encephalitis, Guillain-Barré syndrome or Miller-Fisher syndrome. The route by which SARS-CoV-2 enters the brain and infects neurons remains to be explored, but it starts from binding to a functional receptor of angiotensin-converting enzyme 2 before the virus enters into host cells. In this article we summarize current knowledge from the literature on coronavirus related to SARS-CoV-2 and postulate the possible pathways for SARS-CoV-2 to enter into the brain.

Keywords

Brain, Corona virus, COVID-19, Severe acute respiratory syndrome, SARS-CoV-2

Introduction

COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a newly recognized pandemic disorder. Its typical symptoms usually include fever, cough and difficulty in breathing [1]. Chest imaging shows ground-glass opacities [1]. COVID-19 was initially considered a primary respiratory system disease but eventually it infected multiple systems including cardiovascular [2], gastrointestinal [3, 4], renal [5, 6], hematologic [7-9], as well as the central (CNS) and peripheral (PNS) nervous systems [10-14].

Neurologists have moved to the frontlines [15]. Many patients present with neurological disorders may be infected with SARS-CoV-2 with or without typical COVID-19 classic respiratory symptoms. Current understanding is limited relative to the underlying pathogenesis for SARS-CoV-2 to cause structural and functional abnormalities in the nervous system, which complicates neurologists in efficiently managing neurologic patients with COVID-19. We are facing many clinical challenges with unanswered questions. As neurologists on the frontlines, we are eager to know how SARS-CoV-2 attacks neurons and neural tissues. What evidence do we have to understand how the virus routes into the brain? Why do some, particularly in young, patients with COVID-19 develop strokes [10]? What are the underlying pathophysiologies that would cause COVID-19 patients to die unexpectedly? To help understand SARS-CoV-2 pathogenesis associated with

neurologic disorders and its possible transmissibility routing into the brain and causing COVID-19 neuropathology, we summarize current understanding from laboratory research on coronavirus relevant to SARS-CoV-2 and postulate its possible pathways routing into the brain.

CoVs Overview

There are four subgroups of CoVs, namely, alpha, beta, gamma and delta CoVs. The alpha-CoVs and beta-CoVs infect only mammals causing respiratory illness and gastroenteritis. The gamma-CoVs and delta-CoVs infect birds, but some of them can also infect mammals. All CoVs share similar features in the organization and expression of their genome [16, 17]. Beta-CoVs are highly contagious and include SARS-CoV (or SARS-CoV-1, causing Severe Acute Respiratory Syndrome, or SARS epidemic in Asia and China in 2003), MERS-CoV (causing Middle East Respiratory Syndrome, or camel flu, in 2012) and SARS-CoV-2 (causing COVID-19 pandemic). SARS-CoV-1 and SARS-CoV-2 infect humans sharing the same mechanism initially binding to Angiotensin-Converting Enzyme 2 (ACE2) as a receptor to enter target cells [17, 18], whereas MERS-CoV infects human cells by binding to a different receptor, dipeptidyl peptidase 4 (DPP4, also called CD26) [19].

Our knowledge relative to the transmissibility of SARS-CoV-2 is limited. Since most CoVs have similar structural and infection properties, both SARS-CoV-1 and SARS-CoV-2 share approximately 79.6% identity in the genomes and use the same host receptor ACE2 for cell entry [17, 18], the infection mechanisms previously understood for SARS-CoV-1 may be applicable to SARS-CoV-2. In fact, SARS-CoV-1 and SARS-CoV-2 are similar in many respects comparable clinically in causing symptoms of respiratory diseases as SARS and COVID-19, respectively. However, SARS-CoV-2 has markedly increased infectivity (please see below) [1, 20].

The coronaviral genome encodes four major structural proteins: the spike (S), nucleocapsid, membrane and the envelope proteins [21]. The spike protein is essential for CoVs to enter into the target cells. Sequence analysis of spike protein genome showed 75% identical between the SARS-CoV-2 and SARS-CoV-1 [17]. The spike protein of CoVs is the binding site to ACE2 [16, 21] and comprised of subunits S1 and S2 for receptor binding and membrane fusion, which have important implications in vaccine development.

ACE2 vs. ACE

Both ACE and ACE2 are type 1 integral transmembrane glycoprotein located at the outer cell membrane. ACE2 gene is localized on the chromosome Xp22 [22]. ACE2 was originally identified in testis, heart and kidney. ACE2 is wide spreading in many organs and cells including lungs, arteries, heart, kidney and intestines [23, 24]. Presence of ACE2 protein and mRNA has been demonstrated predominantly in neurons in animal studies, but also has been identified in human postmortem tissue. The highest level of ACE2 has been observed in kidney, lungs and heart [23]. The primary function of ACE2 is to act as a counter balance to ACE, which cleaves angiotensin (Ang) I into the vasoconstricting Ang II which is linked to hypertension. ACE2 in turn cleaves Ang II into the vasodilator Ang 1-7 to lower blood pressure (Figure 1) [25]. Although there are approximately 40% homology between ACE and ACE2, the latter does not convert Ang I to Ang II nor is it blocked by ACE inhibitors [23]. Notably, ACE has two active sites whereas ACE2 has only one. ACE acts as a carboxy-dipeptidase removing two amino acids from C-terminal substrates whereas ACE2 acts as a carboxypeptidase removing a single amino acid. The major substrate for ACE2 is Ang II [23] and ACE2 has a much higher catalytic efficiency for hydrolysis of Ang II (400-fold) compared with Ang I. Ang II interacts with the autonomic nervous system regulating the central and peripheral sensory information.

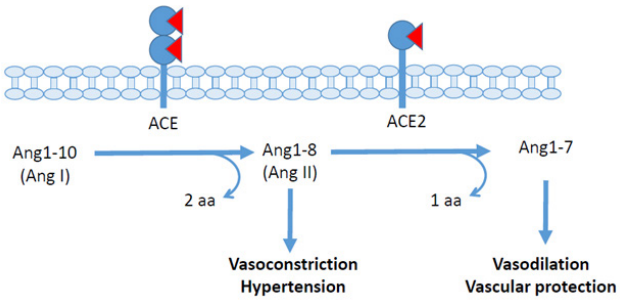

Figure 1: Schematic representation of Angiotensin-Converting Enzyme (ACE) and Angiotensin-converting Enzyme 2 (ACE2). Both ACE and ACE2 are type 1 integral transmembrane glycoproteins located at the outer cell membrane. ACE has two active sites to remove 2 amino acid residues whereas ACE2 has only one to remove one amino acid residue. Ang I (with 1-10 amino acid residues) is cleaved by ACE to yield Ang II (with 1-8 amino acid residues) which is further cleaved by ACE2 to yield Ang1-7 (with 7 amino acid residues).

ACE2 and SARS-CoVs

ACE2 acts as a functional receptor for SARS-CoVs and serves as the main entry point into cells for SARS-CoV-1 [26, 27] and SARS-CoV-2 [28]. Structurally, ACE2 has a short intracellular tail, a transmembrane anchor, and a large ectodomain that constitutes the receptor binding subunit for S1 and membrane-fusing subunit for S2 (Figure 2) [16]. The receptor binding domain of ACE2 has high affinity to the spike S1 protein of the SARS-CoVs [16, 20] and directly binds to the peptidase domain of ACE2 [16], whereas S2 is responsible for membrane fusion [29]. When the spike S1 protein binds to the host receptor of ACE2, another cleavage site is exposed and the S1 is cleaved by host proteases to allow the virus to enter the host cell by membrane fusion, a process that is critical for viral infection [19]. The binding of the spike S1 protein of SARS-CoVs to the enzymatic domain of ACE2 on the surface of cells results in endocytosis and translocation of both the virus and the enzyme into endosomes intracellularly [29]. ACE2 also serves as an entry point into cells for other coronaviruses [27]. TMPRSS2 is a host transmembrane serine protease and is required for SARS-CoV-2 to enter the host cell by cleaving the spike protein and allowing the viral and cellular membranes to fuse [28, 30]. Inhibition of TMPRSS2

may be a potential therapeutic target for vaccine development and is under current investigation. ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells [31]. The affinity of SARS-CoV-2 binding to ACE2 is 10~20 times to that of SARS-CoV-1 [20] which may, in part, correspond to the dramatically increased infectivity of SARS-CoV-2.

There are two forms of ACE2: the full-length form and soluble form (Figure 2). The former is a structural transmembrane domain, its extracellular domain is comprised of receptor-binding domain for the spike protein of SARS-CoVs [17]. The soluble form is cleaved from the extracellular domain of ACE2 by an enzyme known as sheddase. The soluble form is released into the blood stream and ultimately excreted in urine [32]. The soluble form may act as a competitive interceptor of SARS-CoVs by preventing binding of the virus to the receptor-binding domain in the full-length ACE2. *In vitro* studies demonstrated that SARS-CoV-1 replication can be blocked by soluble form of ACE2 in the monkey kidney cell line.

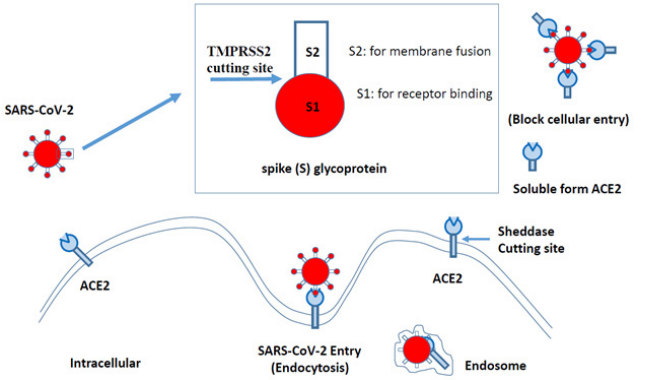

Figure 2: Schematic presentation of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) entry into the cells. Viral spike (S) glycoprotein binds to the receptor of the angiotensin converting enzyme 2 (ACE2) on the cell surface, followed by the proteolytic cut at the S1/S2 junction of the S glycoprotein by the host protease TEMPRSS2. ACE2 on the cell membrane can be cut by a protease sheddase on the host cell membrane to yield soluble form ACE2 which can block SARS-CoV-2 entry.

ACE2 is found in a wide variety of cells including enterocytes of the small intestine, endothelial cells of arteries and veins, arterial smooth muscle cells, epithelial cells of tongue, renal tubular epithelium and Leydig cells in the testes [20, 24, 33]. In the CNS, ACE2 mRNA expression has been demonstrated in the cerebral cortex, striatum, hypothalamus and brainstem [34] and coexists with ACE [35]. The presentation of ACE2 protein in various human organs (oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney and brain) indicates many organs and cells may become targets and victims of SARS-CoV-2. Thus, COVID-19 may be a disorder of multitude, rather than a single respiratory system.

Roads for SARS-CoVs to Invade the Nervous System

Previous studies showed that SARS-CoV-1 is able to infect the CNS, as the virus has been detected in the brains of infected patients, almost exclusively in neurons [36-38]. As aforementioned, human pathogenic coronaviruses SARS-CoV-1 and SARS-CoV-2 invade their target cells through ACE2 [18]. Presence of ACE2 protein and mRNA has been demonstrated predominantly in neurons in animal studies [39], which is widespread throughout the brain and brainstem [40] including the nuclei involving central regulation of cardiovascular function, such as the cardiorespiratory neurons of the brainstem, as well as in non-cardiovascular areas such as the motor cortex and raphe nuclei which have robust functions in the brain including modulating pain, mood, vigilance and levels of consciousness [38, 39].

SARS-CoV-1 may enter the brain via the nose through the olfactory epithelium, as it has been reported in humans and confirmed in animals [40]. This approach of infection may be applicable to SARS-CoV-2 in causing anosmia/hyposmia [41] and attacking brain neurons [11, 12].

An alternative pathway for SARS-CoV-2 to enter the CNS may be hematogenous via the areas of the brain that lack blood-brain barrier such as subfornical organ, the roof of the third and fourth ventricles, capillaries in the pineal gland on the roof of the diencephalon and pineal gland [42], involving transcytosis by leukocytes. Although clinically rare, previous observation in a SARS-patient disclosed that SARS-CoV-1 could be identified in the CSF [41].

Trans-synaptic transfer of SARS-CoV-2 from PNS to CNS may also be possible. Previous animal studies demonstrated that CoVs may first invade peripheral nerve terminals and then gain access to the CNS via a synapse-connected route [43, 44]. The trans-synaptic transfer has been well documented for other CoVs, such as HEV67 [45] and avian bronchitis virus [44, 46]. Following oronasal inoculation to nasal mucosa, CoVs can first be detected in the tonsil, lung and small intestine, and then delivered retrogradely via peripheral nerves to the medullary neurons in animals [44] causing neural infection, in addition to bronchitis or pneumonia, pertinent to critical illness-related conditions [44, 46].

Clinically, patients with neurologic disorders are often elderly who also are vulnerable to COVID-19 with poor outcome due, at least partially, to their comorbidities of aging-related chronic medical conditions [1]. Because of widespread distribution of ACE2 in the brain, neurons are potential targets of SARS-CoV-2. The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes and hypertension, which may facilitate infection with SARS-CoV-2 and predispose the elderly at an increased risk for developing severe and fatal COVID-19 infection [47, 48]. Neurological symptoms seen in patients with COVID-19 range from fairly specific neurologic symptoms such as anosmia/hyposmia (impaired smell) and ageusia/dysgeusia (impaired tasting) [49], myopathy or peripheral nerve injury (e.g. Guillain-Barré syndrome, Miller-Fisher syndrome) [50-52], altered mental status, encephalopathy [14, 53], meningitis [12], encephalitis [14], seizures [1, 13] and stroke [10, 11, 14]; to nonspecific symptoms such as headache, dizziness and fatigue [1, 13].

However, the exact route by which SARS-CoV-2 enters the CNS remains to be explored. Experimental animal studies revealed that SARS-CoV-1 [48] and MERS-CoV [54] could enter the brain, when given intranasally, possibly via the olfactory nerves and thereafter rapidly spread to some specific brain areas including the thalamus and brainstem. In the mice infected with low inoculum doses of MERS-CoV the virus was detected only in the brain, not in the lung, indicating that the infection in the CNS was more important for the high mortality in the infected mice [54]. Among the involved brain areas, the brainstem has been demonstrated to be heavily infected by SARS-CoV-1 [48, 55] or MERS-CoV [54]. Autopsies from patients died of SARS have provided convincing evidence of CNS infection resulting in the detection of SARS-CoV-1 in neurons by electron microscopy, immunohistochemistry, and real-time reverse transcription-polymerase chain reaction [48]. Notably, patients with SARS have been demonstrated the presence of SARS-CoV-1 particles in the brain, where they were located almost exclusively in neurons, no viral particles was detected in nonneuronal cells in the infected human brains [36-38]. In this respect, SARS-CoV-2 may possess a similar mechanism as SARS-CoV-1 to infect neurons via several routes to enter CNS. The pathological findings of the brain caused by SARS-CoV-2 in COVID-19 are urgently needed [11, 12].

Conclusion

In summary, clinical observations and animal studies have shown CoVs infectivity. It may be reasonable to postulate that, because of the similarity in structure and subcellular morphology shared by CoVs, the routes to the brain of other CoVs may be applicable to the recently identified SARS-CoV-2 [55], pending clinical and laboratory verification and confirmation. In this context, understanding transmissibility to the brain would assist healthcare providers better manage patients with COVID-19.

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References

1. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, et al. 2020. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 382: 1708-1720. https://doi.org/10.1056/nejmoa2002032
2. Shi S, Qin M, Shen B, Cai Y, Liu T, et al. 2020. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. https://doi.org/10.1001/jamacardio.2020.0950
3. Wong SH, Lui RN, Sung JJ. 2020. Covid-19 and the digestive system. *J Gastroenterol Hepatol* 35(5): 744-748. https://doi.org/10.1111/jgh.15047
4. Cheung KS, Hung IF, Chan PP, Lung KC, Tso E, et al. 2020. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong cohort and systematic review and meta-analysis. *Gastroenterology* S0016-5085(20): 30448-30450. https://doi.org/10.1053/j.gastro.2020.03.065
5. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, et al. 2020. Presenting characteristics, comorbidities and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA*. https://doi.org/10.1001/jama.2020.6775
6. Durvasula R, Wellington T, McNamara E, Watnick S. 2020. COVID-19 and kidney failure in the acute care setting: our experience from Seattle. *Am J Kidney Dis* S0272-6386(20): 30618-1. https://doi.org/10.1053/j.ajkd.2020.04.001
7. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, et al. 2020. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy and follow-up. *J Am Coll Cardiol* S0735-1097(20)35008-7. https://doi.org/10.1016/j.jacc.2020.04.031
8. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. https://doi.org/10.1111/jth.14869
9. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, et al. 2020. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* S0049-3848(20)30120-1. https://doi.org/10.1016/j.thromres.2020.04.013
10. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, et al. 2020. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med*. https://doi.org/10.1056/nejmc2009787
11. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, et al. 2020. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 201187. https://doi.org/10.1148/radiol.2020201187
12. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 94: 55-58. https://doi.org/10.1016/j.ijid.2020.03.062
13. Mao L, Jin H, Wang M, Hu Y, Chen S, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. https://doi.org/10.1001/jamaneurol.2020.1127
14. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, et al. 2020. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. https://doi.org/10.1056/nejmc2008597
15. Majersik JJ, Reddy VK. 2020. Acute neurology during the COVID-19 pandemic. Supporting the front line. *Neurology*. https://doi.org/10.1212/wnl.0000000000009564
16. Li F. 2016. Structure, function and evolution of coronavirus spike proteins. *Ann Rev Virol* 3(1): 237-261. https://doi.org/10.1146/annurev-virology-110615-042301
17. Lu R, Zhao X, Li J, Niu P, Yang B, et al. 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* 395(10224): 565-574. https://doi.org/10.1016/s0140-6736(20)30251-8
18. Wan Y, Shang J, Graham R, Baric RS, Li F. 2020. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 94(7). https://doi.org/10.1128/jvi.00127-20
19. Lu G, Hu Y, Wang Q, Qi J, Gao F, et al. 2013. Molecular basis of binding between novel human coronavirus MERS- CoV and its receptor CD26. *Nature* 500(7461): 227-231. https://doi.org/10.1038/nature12328
20. Wu C, Zheng M. Single-cell RNA expression profiling shows that ACE2, the putative receptor of COVID-2019, has significant expression in nasal and mouth tissue, and is co-expressed with TMPRSS2 and not co-expressed with SLC6A19 in the tissues. *Infect Dis* https://doi.org/10.21203/rs.3.rs-16992/v1
21. Schoeman D, Fielding BC. 2019. Coronavirus envelope protein: current knowledge. *Virol J* 16(1): 69. https://doi.org/10.1186/s12985-019-1182-0

22. Komatsu T, Suzuki Y, Imai J, Sugano S, Hida M, et al. 2002. Molecular cloning, mRNA expression and chromosomal localization of mouse angiotensin-converting enzyme related carboxypeptidase (mACE2). *DNA Seq* 13(4): 217-220. https://doi.org/10.1080/1042517021000021608
23. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, et al. 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 203(2): 631-637. https://doi.org/10.1002/path.1570
24. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, et al. 2000. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res* 87(5): E1-E9. https://doi.org/10.1161/01.res.87.5.e1
25. Keidar S, Kaplan M, Gamliel-Lazarovich A. 2007. ACE2 of the heart: from angiotensin I to angiotensin (1-7). *Cardiovascul Res* 73(3): 463-469. https://doi.org/10.1016/j.cardiores.2006.09.006
26. Fehr AR, Perlman S. 2015. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol* 1282: 1-23. https://doi.org/10.1007/978-1-4939-2438-7_1
27. Li F. 2013. Receptor recognition and cross-species infections of SARS coronavirus. *Antiviral Res* 100(1): 246-254. https://doi.org/10.1016/j.antiviral.2013.08.014
28. Yan R, Zhang Y, Li Y, Xia L, Guo Y, et al. 2020. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 367(6485): 1444-1448. https://doi.org/10.1126/science.abb2762
29. Millet JK, Whittaker GR. 2018. Physiological and molecular triggers for SARS-CoV membrane fusion and entry into host cells. *Virology* 517: 3-8. https://doi.org/10.1016/j.virol.2017.12.015
30. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, et al. 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181(2): 271.e8-280.e8. https://doi.org/10.1016/j.cell.2020.02.052
31. Lukassen S, Chua RL, Trefzer T, Kahn NC, Schneider MA, et al. 2020. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. EMBO J e105114. https://doi.org/10.15252/embj.20105114
32. Wysocki J, Ye M, Rodriguez E, González-Pacheco FR, Barrios C, et al. 2010. Targeting the degradation of angiotensin ii with recombinant angiotensin-converting enzyme 2: Prevention of angiotensin ii-dependent hypertension. *Hypertension* 55(1): 90-98. https://doi.org/10.1161/hypertensionaha.109.138420
33. Sungnak W, Huang N, Bécavin C, Berg M, Lung HCA, et al. 2020. SARS-CoV-2 entry genes are most highly expressed in nasal goblet and ciliated cells within human airways.
34. Kabbani N, Olds JL. 2020. Does COVID19 infect the brain? If so, smokers might be at a higher risk. *Mol Pharmacol* 97(5): 351-353. https://doi.org/10.1124/molpharm.120.000014
35. Sibony M, Gasc JM, Soubrier F, Alhenc-Gelas F, Corvol P. 1993. Gene expression and tissue localization of the two isoforms of angiotensin I converting enzyme. Hypertension 21(6 Pt 1): 827-835. https://doi.org/10.1161/01.hyp.21.6.827
36. Ding Y, He L, Zhang Q, Huang Z, Che X, et al. 2004. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol* 203(2): 622-630. https://doi.org/10.1002/path.1560
37. Gu J, Gong E, Zhang B, Zheng J, Gao Z, et al. 2005. Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 202(3): 415-424. https://doi.org/10.1084/jem.20050828
38. Xu J, Zhong S, Liu J, Li L, Li Y, et al. 2005. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin Infect Dis* 41(8): 1089-1096. https://doi.org/10.1086/444461
39. Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, et al. 2007. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *Am J Physiol Regul Integr Comp Physiol* 292(1): R373-R381. https://doi.org/10.1152/ajpregu.00292.2006
40. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. 2008. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol* 82(15): 7264-7275. https://doi.org/10.1128/jvi.00737-08
41. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, et al. 2004. Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis* 10(2): 342-344. https://doi.org/10.3201/eid1002.030638
42. Zlokovic BV. 2008. The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* 57(2): 178-201. https://doi.org/10.1016/j.neuron.2008.01.003
43. Li YC, Bai WZ, Hirano N, Hayashida T, Taniguchi T, et al. Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. *J Comp Neurol* 521(1): 203-212. https://doi.org/10.1002/cne.23171
44. Matsuda K, Park CH, Sunden Y, Kimura T, Ochiai K, et al. 2004. The vagus nerve is one route of transneural invasion for intranasally inoculated influenza a virus in mice. *Vet Pathol* 41(2): 101-107. https://doi.org/10.1354/vp.41-2-101
45. McCray PB Jr, Pewe L, Wohlford-Lenane C, Hickey M, Manzel L, et al. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. *J Virol* 81(2): 813-821. https://doi.org/10.1128/jvi.02012-06
46. Zochodne DW. SARS, SIRS, and neurological disease. *Arch Neurol* 61(11): 1647-1648. https://doi.org/10.1001/archneur.61.11.1647
47. Fang L, Karakiulakis G, Roth M. 2020. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 8(4): e21. https://doi.org/10.1016/s2213-2600(20)30116-8
48. Lin Z, Chen Y, Zhang W, Chen AF, Lin S, et al. 2008. RNA interference shows interactions between mouse brainstem angiotensin AT1 receptors and angiotensin-converting enzyme 2. *Exp Physiol* 93(5): 676-684. https://doi.org/10.1113/expphysiol.2007.041657
49. Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, et al. 2020. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA*. https://doi.org/10.1001/jama.2020.6771
50. Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, Pedro-Murillo ES, Bermejo-Guerrero L, et al. 2020. Miller fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology* 10.1212/WNL.0000000000009619. https://doi.org/10.1212/wnl.0000000000009619
51. Zhao H, Shen D, Zhou H, Liu J, Chen S. 2020. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol* 19(5): 383-384. https://doi.org/10.1016/s1474-4422(20)30109-5
52. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, et al. Guillain-Barré syndrome associated with SARS-CoV-2. *N Engl J Med*. https://doi.org/10.1056/nejmc2009191
53. Filatov A, Sharma P, Hindi F, Espinosa PS. 2020. Neurological complications of coronavirus disease (COVID-19): encephalopathy. *Cureus* 12(3): e7352. https://doi.org/10.7759/cureus.7352
54. Li K, Wohlford-Lenane C, Perlman S, Zhao J, Jewell AK, et al. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *J Infect Dis* 213(5): 712-722. https://doi.org/10.1093/infdis/jiv499
55. Luo JJ, Dun N. 2020. Basic knowledge for neurologists: SARS-CoV-2 and COVID-19. Are we well prepared for taking care of our patients? *J Neurol Exp Neurosci* 6(S1): S1-S3. https://doi.org/10.17756/jnen.2020-S1-001